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New Rhodacyclopentanone-Based Methodologies and Studies Towards the Total Synthesis of Otonecine-Type Pyrrolizidine Alkaloids

New Rhodacyclopentanone-Based Methodologies and Studies Towards the Total Synthesis of Otonecine-Type Alkaloids

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(110098 words)

Author’s Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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Date:

Abstract

Processes for the synthesis of seven-membered *N*-heterocycles, involving intramolecular nucleophilic addition to rhodacyclopentanones have been developed. Initially, a (6+1) carbonylative cyclisation of cyclopropylureas, discovered by Dr. McCreanor at Bristol, was optimised and its scope examined. Mechanistic studies were carried out to explain unexpected aspects of this reaction. Subsequently, investigations were directed towards the discovery of other processes involving nucleophilic addition to rhodacyclopentanones, which resulted in the identification of a (6+1) carbonylative cyclisation of cyclopropylmethylamides to form azepanes.

Later, studies were directed towards the asymmetric total synthesis of (*R*)-otonecine and related pyrrolizidine alkaloids. This built upon the (7+1) carbonylative cycloaddition of cyclopropylacrylamides to form azocanes, developed at Bristol. Further optimisation of the (7+1) reaction conditions identified several beneficial amide and carboxylic acid additives, and an improved reaction set-up, which allowed the cycloaddition of a challenging silylmethylcyclopropane-based substrate. Investigations into the four proposed post-cycloaddition transformations identified suitable conditions for three of these. A Rubottom oxidation and Tamao-Fleming oxidation installed the C7- and C9-alcohols of otonecine. The C2 to C1 alkene isomerisation was achieved under kinetic conditions using newly developed conditions for the hydrobromination of enelactams. The penultimate lactam reduction step failed under various chemoselective conditions.

In parallel studies, a short, asymmetric and diastereodivergent synthesis of the C_{10} dicarboxylic necic acids was designed. Unoptimised conditions for the asymmetric crotylation of a pyruvate ester formed the C12,C13-vicinal stereocentres of the necic acid targets. Finally, model studies into a sp^2-sp^3 Negishi cross-coupling suggest that this transformation might be applicable to the proposed synthesis. Realisation of the asymmetric total synthesis of (*R*)-otonecine and the C_{10} dicarboxylic necic acids pave the way for the first total synthesis of other otonecine-type pyrrolizidine alkaloids.

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First of all, I would like to thank Professor John Bower for his support and guidance. John has been a dedicated mentor over the past few years, who has reliably set aside his own time to provide advice and solutions to my questions. From the start of my PhD to writing my thesis, John has pushed me to improve in every aspect of chemistry for which I am extremely grateful. I have no doubt that I am a stronger and more confident chemist having been in the Bower lab.

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A special thank you to the following, who have been so easy to work with, and laugh at: Ian Hazelden, Lauren O'Neil, Olivia Boyd, Josh (Jash) Farndon, Jamie Cadge and are Tim Aldous. And the boys themselves, Andrew Dalling and Ben Jones, for being so easily persuaded to have a drink and being fully on board with even the riskiest of pranks. I will miss our regular pub sessions, dinner parties, Jamie's shirts, and the way Ben's eyes get smaller as he drinks.

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Table of Contents

Abbreviations

ACP	Alkylidenecyclopropane
Acr	9-mesityl-10-methylacridinium
AIBN	azobisisobutyronitrile
BARF	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BDMS	benzyl(dimethyl)silyl
BHT	2,6-di-*tert*-butyl-4-methylphenol
CO	carbon monoxide
cod	cyclooctadiene
Cp	cyclopentadienyl
***m*-CPBA**	*m*-chloroperoxybenzoic acid
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
dppe	bis(diphenylphosphino)ethane
dppm	bis(diphenylphosphino)methane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
1,2-DCB	1,2-dichlorobenzene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
1,2-DCE	1,2-dichloroethane
DFT	density functional theory
DG	directing group
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
1,2-DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
d.r.	diastereomer ratio
e.e.	enantiomeric excess
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraaceticacid

EWG	electron-withdrawing group
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMPA	hexamethylphosphoramide
IMes	1,3-dimesitylimidazol-2-ylidene
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
MW	molecular weight
MTM	methylthiomethyl
NBS	*N*-bromosuccinimide
1-Npth	1-naphthyl
Nu	nucleophile
PA	pyrrolizidine alkaloid
PCC	pyridinium chlorochromate
r.r.	regioisomer ratio
SET	single electron transfer
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSE	(trimethylsilyl)ethyl
pTSA	*p*-toluenesulfonic acid
UHP	ureahydrogen peroxide
VCP	vinyl cyclopropane

Chapter 1 – Introduction

1.1 Tackling the declining rate of drug discovery

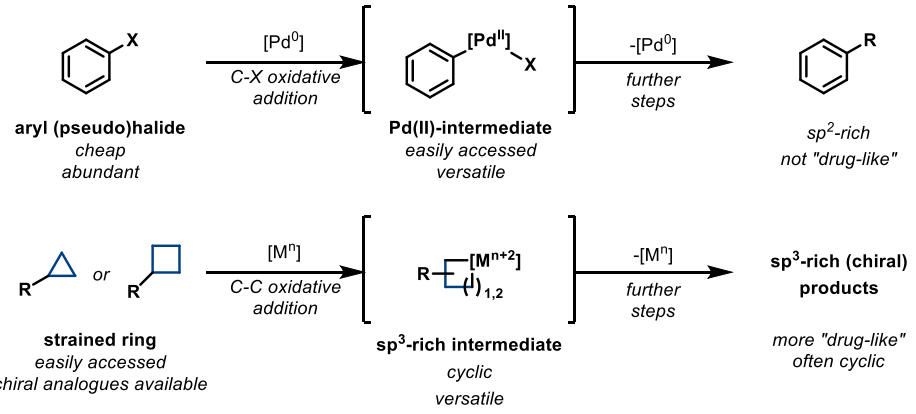
Since the 1990s, the pharmaceutical industry has suffered a steady decline in productivity as measured by the number of novel drugs released onto the market each year.[1-3] This observation is starkly illustrated by the fact that in the period from 2010 to 2017, greater than 93% of drug candidates entering Phase 1 clinical trials failed to reach the market.[4] The remarkable inefficiency of the drug discovery process has forced pharmaceutical companies to adopt cost saving measures, which are not conducive to developing treatments for many diseases.[1] For example, less money is being reinvested into basic (but high risk) research and development, which is necessary to address so far untreatable diseases. Instead, research focus is gradually shifting towards low risk therapeutic areas, for which effective treatments may already exist. Furthermore, the need to recoup costs, which were lost to failed drug candidates, is a factor in rising drug prices.

The underlying causes of declining drug approval rates have been studied. In the 1990s, approximately 40% of failures were due to compounds having poor pharmacokinetic properties and bioavailability, which was in part a result of the adoption of high-throughput screening (HTS) methods in the early stages of the drug discovery process.[1] The compound libraries employed in these HTS efforts were heavily skewed towards sp^2-rich compounds as a result of the explosive development and uptake of transition metal-catalysed cross-coupling methodologies, such as the Suzuki coupling.[5] In response, several new compound metrics (e.g. MW, clogP, Lipinski's rule of 5) were introduced to help measure the drug-likeness of a molecule.[6-9] These metrics were successful in improving the physical properties of drug libraries, but did not result in an increase in drug approvals. Instead, toxicity became the number one reason why drug candidates failed in clinical trials.[10] Modern drug discovery programmes now put a large emphasis on investigating the toxicity of compounds prior to their introduction into the clinic, but the causes of toxicity are poorly understood.[11]

In 2008, Lovering and co-workers introduced fractional sp^3 character (Fsp^3, the fraction of sp^3 carbons out of the total number of carbon atoms in a molecule) as a measure of a molecule's degree of saturation, which is related to the "chirality" of that molecule.[12] The authors observed that the average Fsp^3 character of clinical candidates increased at each stage of the drug discovery process (31% increase from preclinical to market) indicating that sp^3-rich molecules were more successful in the clinic. In 2013, Lovering furthered this analysis of small molecules in clinical trials, and concluded that compounds with greater Fsp^3 values were less likely to cause off-target toxicity.[13] It was concluded from these two studies that compounds with greater Fsp^3 values (and therefore more stereocentres) are better suited to binding to the 3-dimensional binding sites of their biological target, resulting in a high

binding affinity. Furthermore, these molecules are innately more specific to a single binding site, which reduces the chances that they will exhibit off-target toxicity.

In order to increase the average Fsp^3 value of molecules produced by medicinal chemists, it is desirable to develop new catalytic methodologies that are as appealing to medicinal chemists as, for example, the Suzuki reaction.[5, 14] The success of Pd(0)-catalysed cross couplings is partly due to the accessibility and utility of Pd(II)-intermediates (Scheme 1). These can be reliably generated by oxidative addition of a Pd(0)-catalyst to readily available aryl (or alkenyl) (pseudo)halides. The resulting Pd(II)-intermediate can be directed to several different catalytic steps giving access to many product types. Therefore, one way of improving the average Fsp^3 value of drug libraries would be to develop analogous *sp^3-rich* organometallic intermediates, which are as easy to access and as versatile as Pd(II)-intermediates. Towards this end, several research groups have developed catalytic methodologies that exploit oxidative addition to highly strained C-C bonds of small rings (cyclopropane or cyclobutane derivatives) to generate sp^3-rich intermediates, which can then be converted to sp^3-rich products. In particular, oxidative addition of transition metals to C-C bonds of small rings initially forms cyclic intermediates, which are particularly suited to the synthesis of (hetero)cyclic molecules. Research at Bristol has contributed to this field with the development of a directing-group strategy for the formation of rhodacyclopentanones from cyclopropane derivatives (see Section 1.3). Rhodacyclopentanones formed in this way have been shown to be useful for the synthesis of complex sp^3-rich heterocyclic structures.



Scheme 1: Comparison of a Pd(II)-intermediate with strained ring-derived organometallics.

The following sections will introduce the field of transition metal-catalysed C-C oxidative addition to strained small rings, and how this basic step has been incorporated into the synthesis of sp^3-rich products. The discussion will focus on recent developments (from mid-2009 to mid-2019) in order to present the state of the art, but seminal contributions from before this time period will be included where informative. Transition metal-catalysed C-C cleavage of small rings can also be achieved *via* redox neutral β-carbon elimination processes, but these will not be discussed here because

they are not pertinent to the research contained within this dissertation. This area has been reviewed recently.[15] In Section 1.3, a strategy for directed C-C oxidative addition to cyclopropanes, developed at Bristol, is described. Finally, the aims of the research project will be presented.

1.2 Oxidative addition of transition metals to strained C-C bonds

Aspects of this Chapter have been adapted from a review article.

(Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev*. **2017**, *117*, 9404)

Oxidative addition of transition metals to strained C-C bonds (herein also termed as "transition-metal"-addition) is an established process.[16-17] Cyclopropanes are particularly suited to C-C oxidative addition by transition metals because of two main reasons. Firstly, C-C oxidative insertion is promoted by the release of ring strain, which acts as a thermodynamic and kinetic driving force.[18] Secondly, the HOMO and LUMO orbitals of cyclopropanes (and to a lesser extent cyclobutanes) have significant p-character, which makes them suited to bonding with transition metal HOMOs and LUMOs (Figure 1A).[18] The p-orbital character is a result of the narrow bond angles within the cyclopropane ring causing the C-C bonds to be twisted out of linearity giving them the appearance of "banana bonds". The first example of C-C oxidative addition to a cyclopropane was achieved in 1955 by Tipper and Lawrence who reported the oxidative addition of $PtCl_2$ to cyclopropane to form a platinacyclobutane.[19-20] Since then, several categories of strained, small rings have been employed in C-C oxidative addition-based methodologies (Figure 1B). Cyclopropenes (approximate strain energies of 55 kcal/mol)[21-22] and alkylidenecyclopropanes (approximate strain energies of 39 kcal/mol)[21] possess the greatest ring strain of the three-membered rings as they contain sp^2-hybridised ring carbons, and therefore readily undergo C-C oxidative addition by transition metals. Less strained cyclopropanes, such as vinyl cyclopropanes, and cyclopropyl ketones and their derivatives, have also proved viable. C-C oxidative addition to less

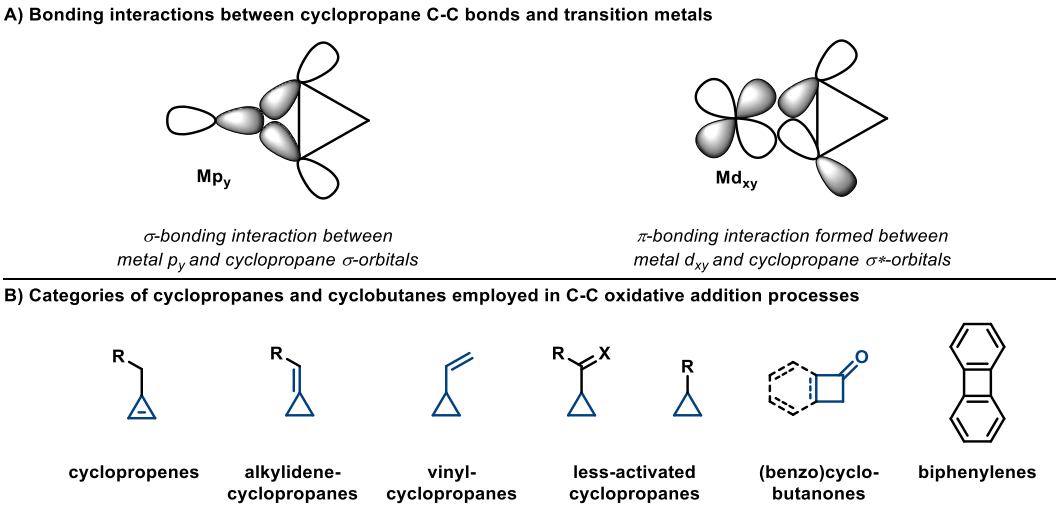


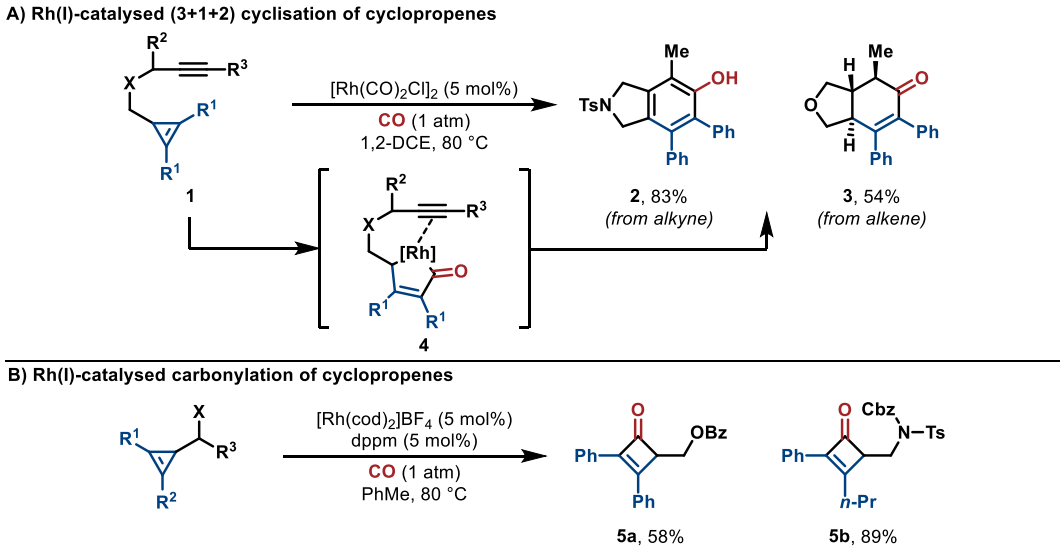
Figure 1

activated cyclopropanes (approximate strain energies of 28 kcal/mol)[22] is more challenging, but strategies have emerged in the recent decades. Four-membered rings are challenging in this context because these are typically less strained than three-membered rings,[22] but strained cyclobutane analogues possessing sp^2-hybridised ring atoms, such as biphenylenes and cyclobutanones, have found use in a number of contexts.

1.2.1 Cyclopropane-based processes

1.2.1.1 Cyclopropenes

Cyclopropenes are among the most strained (approximate strain energy 55 kcal/mol) of the cyclopropane-based systems and are therefore highly susceptible to C-C activation by transition-metals.[21] However, few examples of cyclopropene-based methodologies exist, perhaps due to the lack of methods for the synthesis of cyclopropenes. Wang and co-workers have published Rh(I)-catalysed methodologies based on C-C addition to cyclopropenes.[23] One example, published in 2010, describes a Rh(I)-catalysed carbonylative (3+1+2) cycloaddition of cyclopropenes **1**, which forms 5,6-heterobicycles (e.g. **2** and **3**) (Scheme 2A).[24] The transformation is initiated by oxidative addition to the C-C single bond of the cyclopropene, followed by migratory insertion of carbon monoxide (CO) to form rhodacyclopentenones **4**. Migratory insertion of the tethered π-unsaturate and C-C reductive elimination forms the products. Carbon monoxide has been incorporated as a one-carbon component in many related C-C activation-based methodologies described herein. More recently, Li and co-workers demonstrated that rhodacyclopentenones (cf. **4**) could also undergo reductive elimination to form cyclobutenones (e.g. **5a** and **5b**) (Scheme 2B).[25] These examples show how organometallic intermediates can be redirected to different mechanistic pathways resulting in the synthesis of structurally diverse products.

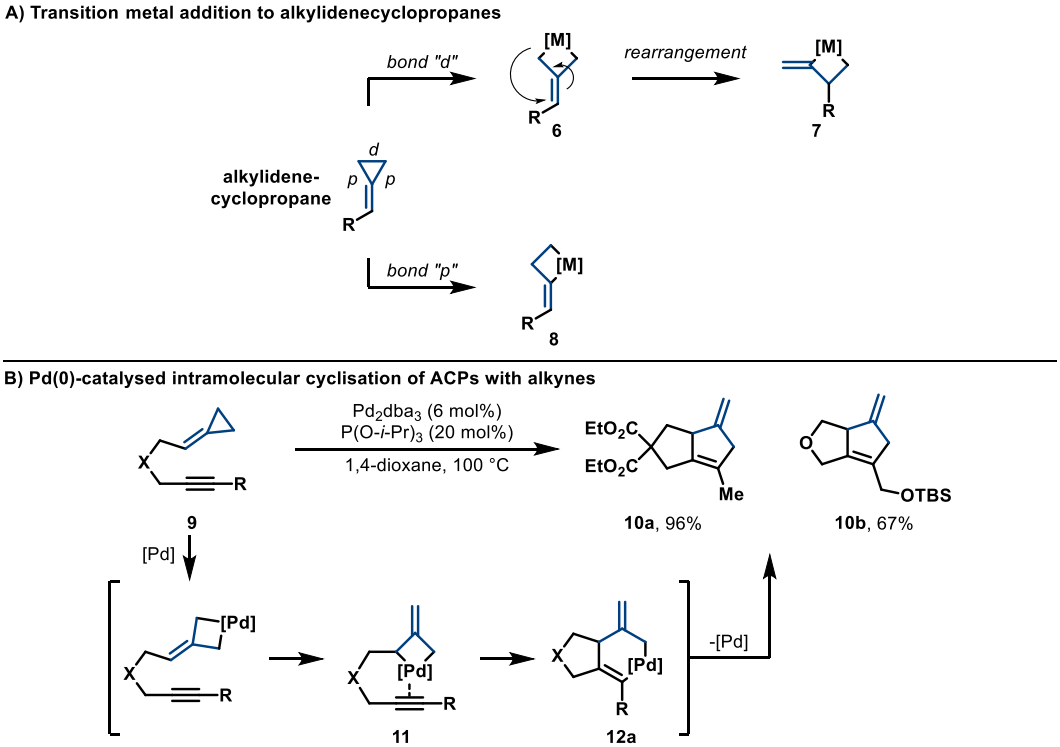


Scheme 2

1.2.1.2 Alkylidenecyclopropanes

Alkylidenecyclopropanes (ACPs) are another class of highly strained (approximate strain energy 39 kcal/mol) cyclopropane-based system, which undergo facile C-C oxidative addition by transition metals.[21] Metal addition can occur to either the distal (bond "*d*") or proximal (bond "*p*") C-C bond leading to regioisomeric metallacyclobutanes **6** or **8**, respectively (Scheme 3A). Metallacyclobutane **6**, resulting from addition to the distal C-C bond, undergoes allylic rearrangement to form the more stable isomer **7**. Both **6** and **8** have been implicated in processes described herein. The regioselectivity of C-C oxidative addition to ACPs is influenced by the transition metal and by other factors such as the ligand. As a result, distinct product scaffolds can be accessed from ACP-based substrates depending on the catalyst system employed.

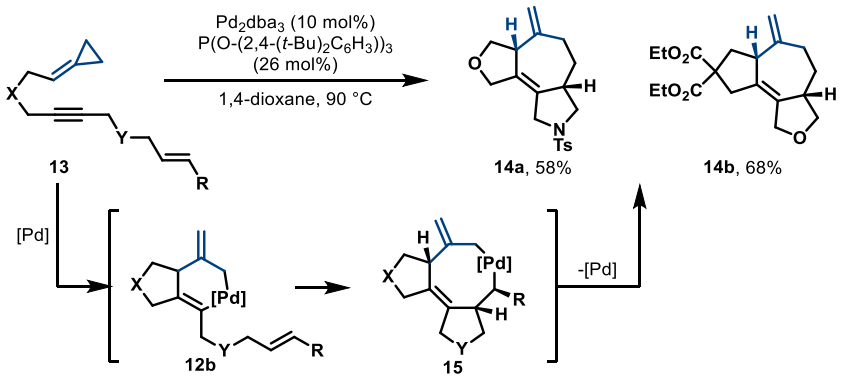
The Mascareñas group have developed a suite of ACP-based methodologies, which demonstrate how a single organometallic intermediate (see **12a**) can give rise to multiple product scaffolds by controlling the subsequent catalytic steps. In 2003, a protocol for the Pd(0)-catalysed (3+2) cycloaddition of ACPs **9** to form 5,5-bicycles (e.g. **10a** and **10b**) was published (Scheme 3B).[26] Computational studies support the proposed mechanism, which involves initial Pd(0)-addition to the distal C-C bond of ACPs **9** and rearrangement to give isomer **11**.[27] Carbopalladation of the tethered alkyne forms six-membered palladacycle **12a**, from which reductive elimination affords the observed products. It has since been shown that palladacycle **12a** can be generated enantioselectively by using a chiral phosphoramidite ligand.[28] Several further developments were reported,[29-30] including the use of



Scheme 3

substrates bearing tethered alkenes,[31] allenes[32] and 1,3-dienes,[33] each of which resulted in the formation of a different product scaffold.

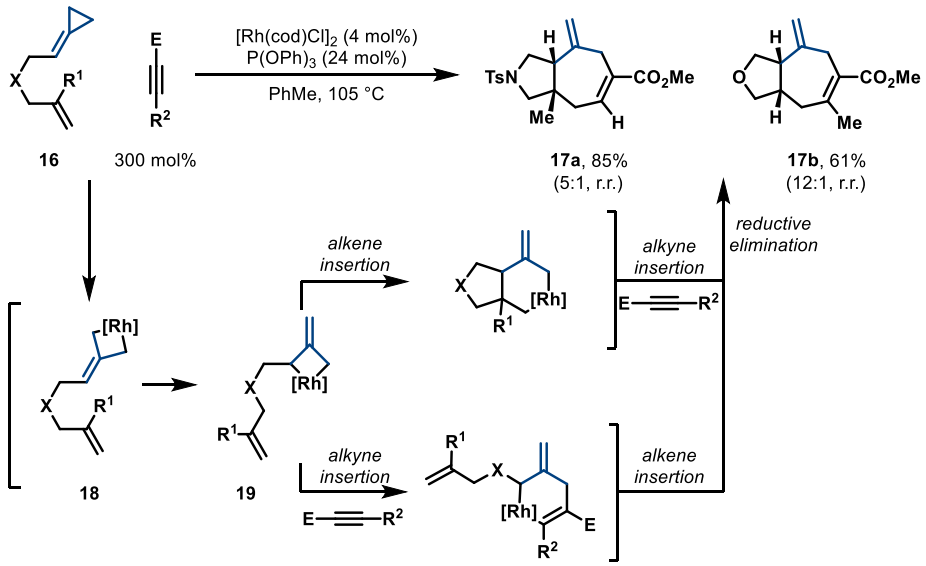
Mascareñas and co-workers later demonstrated that six-membered palladacycle **12b** (cf. **12a**) could be redirected to undergo further complexity generating steps instead of C-C reductive elimination. For example, ACPs **13**, bearing two tethered π-unsaturates, underwent (3+2+2) cycloaddition when treated with a phosphine-ligated Pd(0)-catalyst to form 5,7,5-tricycles (e.g. **14a** and **14b**) (Scheme 4).[34] Here, palladacycle **12b** undergoes carbopalladation of the tethered alkene (instead of C-C reductive elimination) to form eight-membered intermediate **15**. Reductive elimination then provided the observed 5,7,5-tricycles. The Pd(0)-catalysed conditions suffered from competing formation of (3+2) side-products (*via* reductive elimination from **12b**); this prompted the development of Rh(I)-catalysed conditions, which completely favoured the formation of the (3+2+2) cycloaddition products.[35-36]



Scheme 4: Pd(0)-catalysed (3+2+2) cycloaddition of ACPs.

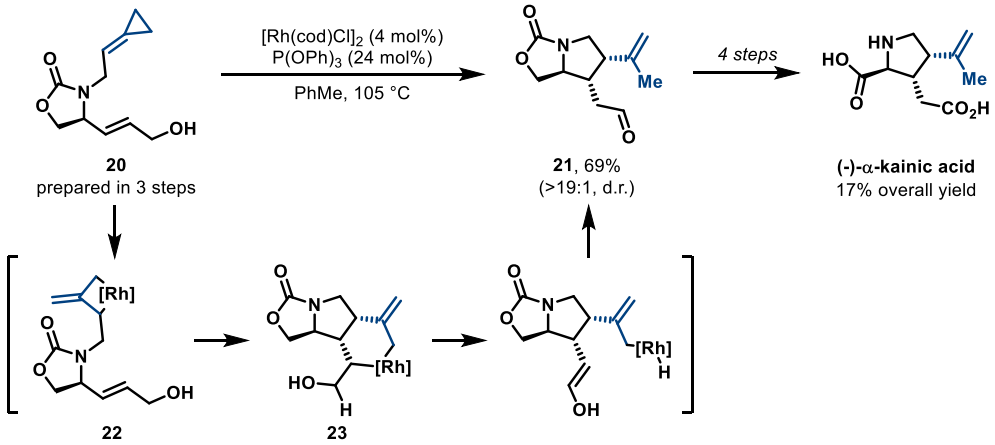
In 2008, Evans and Inglesby published a Rh(I)-catalysed *intermolecular* (3+2+2) cycloaddition of ACPs **16** with external electron-deficient alkynes to form 5,7-bicycles (e.g. **17a** and **17b**) (Scheme 5).[37] In this case, the Rh(I)-catalyst inserts into the distal C-C bond of ACP **16** to form rhodacyclobutane **18**, which rearranges to **19**. Next, an undetermined order of consecutive carbometallations of the alkene and alkyne (the regiodetermining step) is followed by reductive elimination to give the observed products with moderate to good levels of regioselectivity (4:1 to >19:1 r.r.). Later, trialkoxysilane-substituted alkenes were identified as efficient substrates in this transformation,[38] and the methodology was incorporated into a three step total synthesis of the sesquiterpene, pyrovellerolactone.[39]

In the absence of an external alkyne, ACPs can undergo (3+2) ene-cycloadditions to form substituted pyrrolidines. This transformation was demonstrated by the Evans group in the total synthesis of (-)-α-kainic acid (Scheme 6).[40] Treatment of ACP **20** (prepared in three steps from serine) with a phosphite-ligated Rh(I)-catalyst afforded pyrrolidine **21** in 69% yield and as a single diastereomer *via* a (3+2) ene-cycloaddition. The mechanism of the Rh(I)-catalysed (3+2) ene-cycloaddition begins with the formation of rhodacyclobutane **22**, which carbometallates the alkene. The resulting rhodacycle **23**



Scheme 5: Rh(I)-catalysed (3+2+2) cycloaddition of ACPs wtith external alkynes

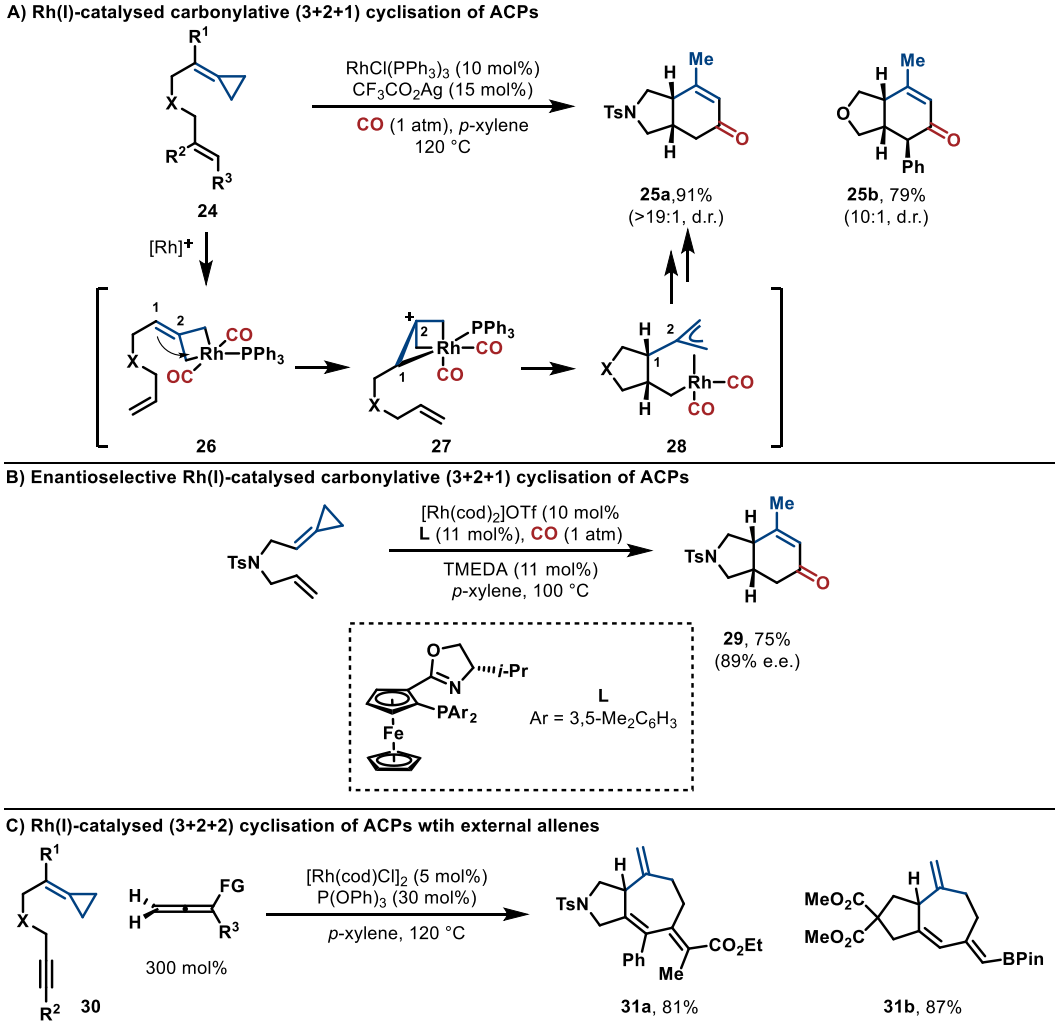
undergoes β-hydride elimination from the exocyclic position followed by C-H reductive elimination to afford pyrrolidine **21**. This was advanced to (-)-α-kainic acid in four steps. More recently, Evans and co-workers demonstrated that rhodacycles related to **23**, containing β-sulfide moieties, undergo competitive β-sulfide elimination to provide allylsulfur-substituted five-membered rings.[41]



Scheme 6: Rh(I)-catalysed (3+2) cycloaddition of ACP **20** in the total synthesis of (-)-α-kainic acid.

Evans and co-workers have also shown that carbon monoxide can serve as a single-carbon component in Rh(I)-catalysed (3+1+2) cycloadditions of ACPs **24** to form 5,6-heterocycles (e.g. **25a** and **25b**) (Scheme 7A).[42] Computational studies suggest that the initially formed rhodacyclobutane **26** isomerises *via* trimethelenemethane complex **27** to form Rh(III)-allyl species **28**. Note that Ni-analogues of trimethelenemethane complex **27** have been ruled out as intermediates in related transformations.[43-44] Rh(III)-allyl species **28** undergoes carbonylation and reductive elimination to afford the observed products. In the presence of a chiral *P*,*N*-ligand, good levels of enantioselectivity

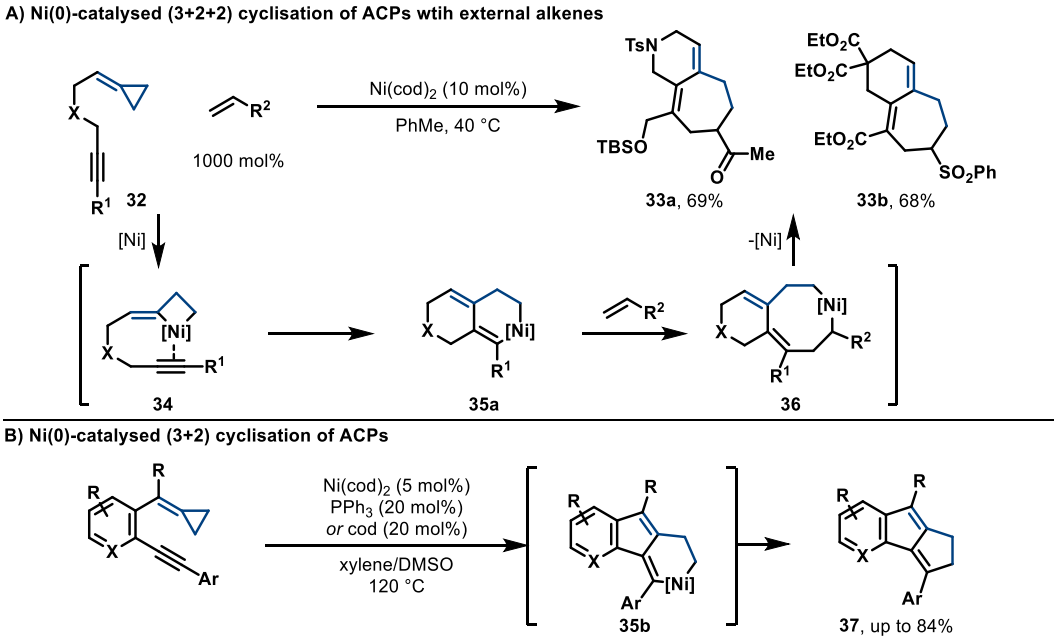
(e.g. 89% e.e. for **29**) were achieved (Scheme 7B). Kim and Chung disclosed a related procedure in which tethered alkynes are used to make phenols.[45] Further investigations into the mechanism of (3+1+2) cycloadditions of ACPs resulted in the isolation of a neutral Rh(III)-complex, related to trimethelenemethane **27**, which proved to be catalytically competent.[46] Ultimately this led to the development of (3+2+2) cycloadditions of ACPs **30** with external allenes to form 5,7-bicycles containing tri- and tetrasubstituted alkenes (e.g. **31a** and **31b**) (Scheme 7C).[47] Additionally, by increasing the alkyne tether length, 6,7-heterocycles could be accessed using this methodology.



Scheme 7

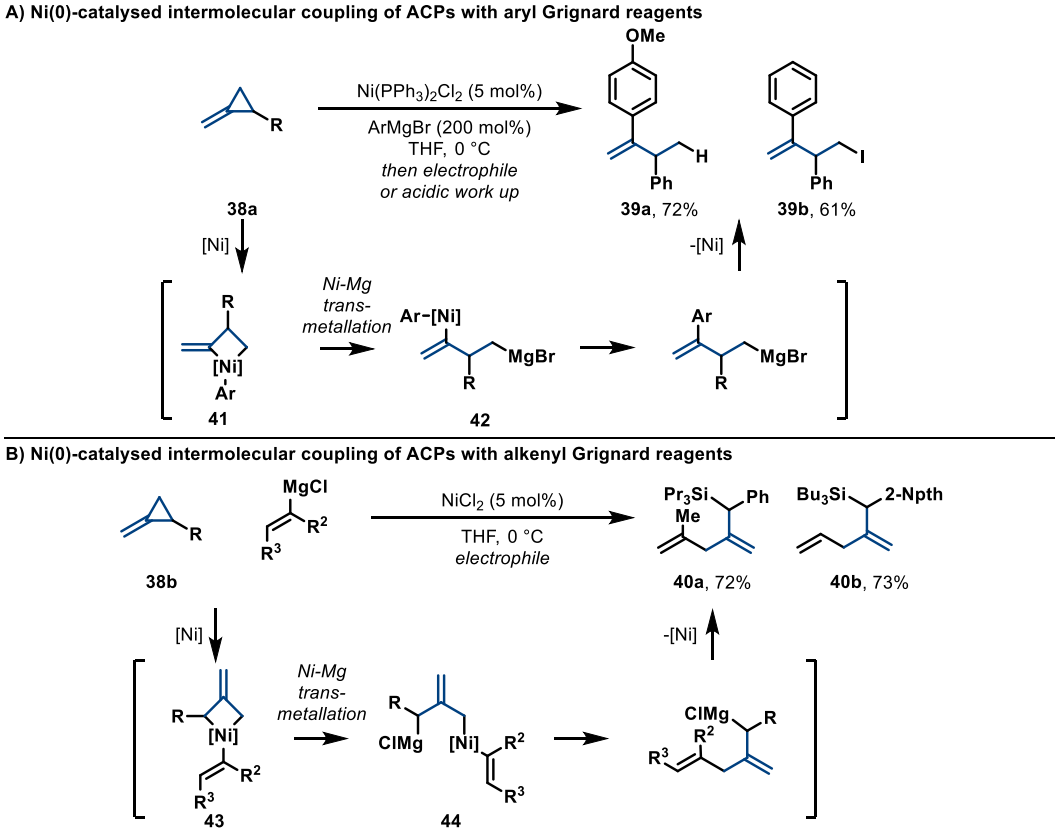
It has been known since the 1970s that Ni(0)-catalysts tend to undergo oxidative addition to the proximal C-C bonds of ACPs, which is in contrast to the Rh(I)- and Pd(0)-catalysed reactions discussed so far.[43-44] Consequently, ACP-based substrates can afford different product scaffolds depending on the catalytic system employed. Mascareñas and co-workers demonstrated this effect in a Ni(0)-catalysed (3+2+2) cycloaddition of ACPs **32** with external alkenes to form 6,7-bicycles **33a/b** (Scheme 8A).[48] Computational studies indicate that Ni(0)-addition to the proximal C-C bond of ACPs **32** is directed by the tethered alkyne. The resulting nickelacycle **34** undergoes consecutive alkyne and alkene

carbometallation to provide intermediate **35a**. Reductive elimination from **35** affords 6,7-bicyclic products. Subsequent reports have expanded on the synthetic utility of nickelacycles related to **35a**.[49] Included in these reports is an example by Zhang and co-workers whereby reductive elimination from nickelacycle **35b** provides aryl-fused products **37** (Scheme 8B).[50]



Scheme 8

Subtle changes to the catalytic system have been found to influence the regioselectivity of Ni(0)-addition to ACPs. For example, Kambe, Terao and co-workers reported that a phosphine-ligated Ni(0)-catalyst inserts into the proximal C-C bond of simple ACPs **38a**, which, in the presence of aryl Grignard reagents, leads to the formation of α-substituted styrenes (e.g. **39a** and **39b**) (Scheme 9A). In contrast, $NiCl_2$-based conditions (i.e. in the absence of a phosphine ligand) initiate by Ni(0)-addition to the *distal* C-C bond of simple ACPs **38b** resulting in the formation of 1,4-dienes (e.g. **40a** and **40b**) when coupled with vinyl Grignard reagents (Scheme 9B). Both transformations involve Ni-Mg transmetallation of the corresponding nickelacyclobutane (**41** or **43**) to form bimetallic intermediates (**42** or **44**). Reductive elimination from the Ni(II)-moiety affords a Grignard reagent, which is quenched by the addition of an electrophile. More recently, intermolecular hydroamidation of ACPs has been reported[51] in which a Pd(0)-catalyst inserts into the distal C-C bond.[52]



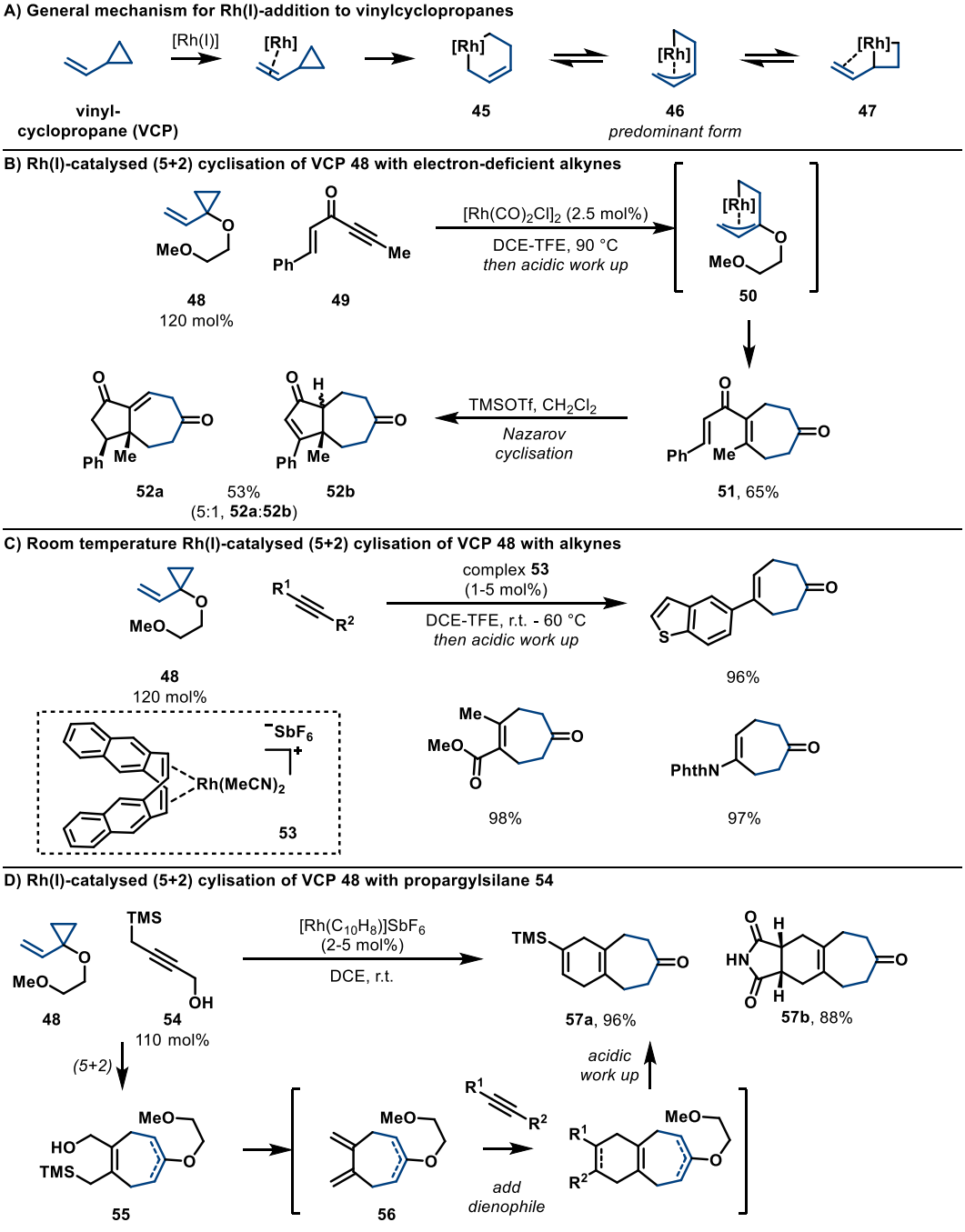
Scheme 9

1.2.1.3 Vinylcyclopropanes

Saturated cyclopropanes are less strained than the cyclopropenes or alkylidenecyclopropanes discussed so far, and are therefore less reactive towards oxidative addition by transition metals.[21] However, adjacent unsaturation, as is present in vinylcyclopropanes (VCPs), serves to activate the cyclopropane to C-C oxidative addition. Seminal studies by Wender and co-workers introduced VCPs as five-carbon components in Rh(I)-catalysed (5+2) cycloadditions, and this strategy has resulted in the development of a suite of synthetic methods.[53-55] A general mechanism for the reaction between VCPs and Rh(I)-catalysts is depicted in Scheme 10A. Initially, Rh(I)-coordination to the π-bond of the VCP triggers oxidative addition to the cyclopropane, forming Rh(III)-allyl intermediates **46**. These intermediates can act as either a five-carbon component (i.e. *via* species **45**) or a three-carbon component (i.e. *via* species **47**) in subsequent processes.

Wender and co-workers introduced alkoxy-substituted VCP **48** as a five-carbon component in (5+2) cycloadditions (Scheme 10B). Upon cyclisation, the alkoxy-substituent of VCP **48** is incorporated as an enol ether moiety, which can then be hydrolysed to unveil a ketone.[56-59] For example, under Rh(I)-catalysis, VCP **48** can undergo a (5+2) cycloaddition with electron-deficient alkynes to form seven-membered divinylketones (e.g. **51**) upon hydrolysis of the initially formed enol ether (not shown).[60] Divinylketones of this type are primed for Lewis-acid promoted Nazarov cyclisations to form 5,7-

carbocycles (e.g. **52a** and **52b**). The mechanism of the (5+2) cycloaddition of VCP **48** and external alkynes **49** is proposed to begin with the formation of Rh(III)-allyl species **50**. This carbometallates the external alkyne, and subsequent reductive elimination forms the seven-membered ring. The mechanism has since been studied by computational methods,[61] and a Rh(III)-allyl complex analogous to **50** has been isolated and characterised by X-ray crystallography.[62]

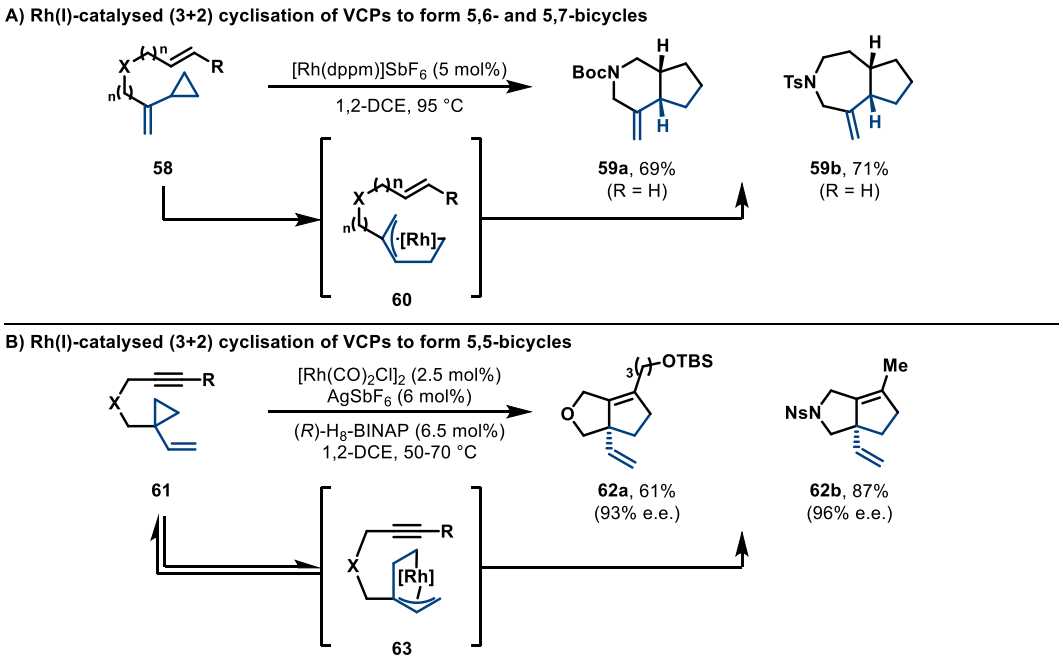


Scheme 10

A key breakthrough in the application of VCPs in C-C activation methodologies was the discovery of superior *cationic* Rh(I)-catalysts, which allowed related transformations to proceed at

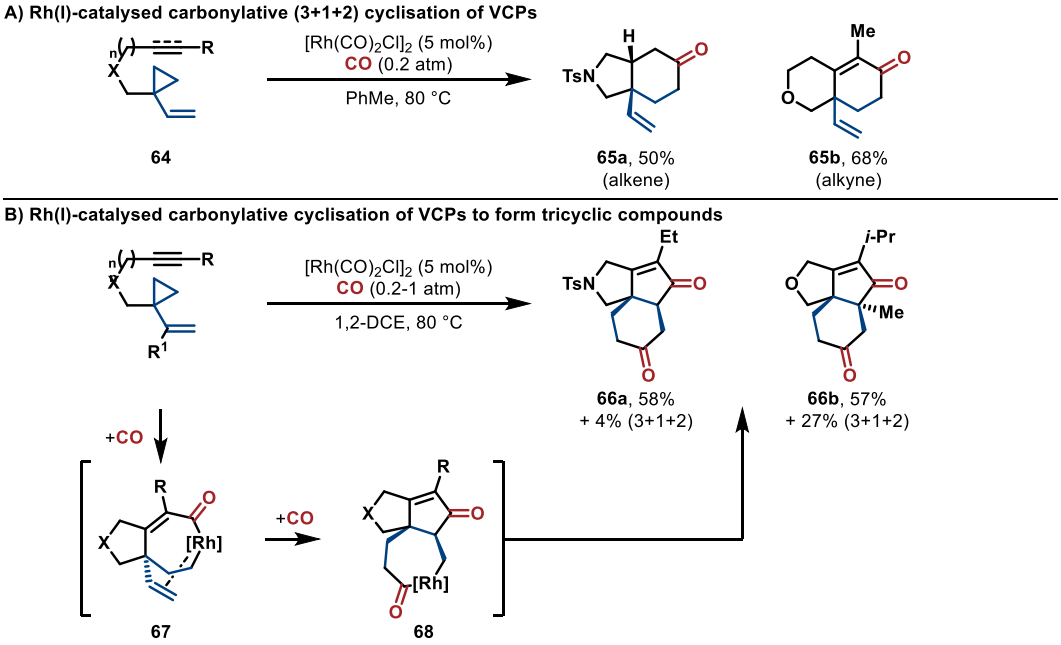
room temperature.[63-64] This ultimately led to the development of cationic Rh(I)-catalyst **53**, which is a highly efficient catalyst for a variety of VCP-based protocols including the (5+2) cycloaddition of VCP **48** with non-polarised alkynes (Scheme 10C).[65-66] Further contributions from Wender and co-workers include the application of propargylsilanes as two-carbon components in (5+2) cycloadditions. Here, cyclic allylsilanes are formed and these can undergo further complexity generating transformations.[67] For example, (5+2) cycloaddition of VCP **48** with propargylsilane **54** (bearing an additional propargylic alcohol) provided allylsilane **55** (Scheme 10D).[68] This then underwent an acid-mediated vinylogous-Petersen elimination to afford dienes **56**, which took part in a (Rh-catalysed or thermal) Diels-Alder cycloaddition with an added dienophile providing cycloadducts (e.g. **57a** and **57b**).

Yu and co-workers have utilised VCPs as three-carbon components in cycloaddition reactions. For example, Rh(I)-catalysed (3+2) cycloaddition of VCPs **58**, bearing tethered alkenes, afforded 5,6- and 5,7-heterocycles (e.g. **59a** and **59b**) (Scheme 11A).[69] Here, Rh(I)-addition to VCP **58** forms Rh(III)-allyl intermediate **60** in an identical manner to the previous methodologies. However, subsequent intramolecular carbometallation proceeds such that only the cyclopropane carbons are incorporated into the newly formed cyclopentane ring. Potential (5+2) cycloaddition products were not observed. 1,1-Disubstituted VCPs **61** undergo a similar enantioselective (3+2) cycloaddition when treated with a cationic (*R*)-H8-BINAP-ligated Rh(I)-catalyst thus affording 5,5-heterobicycles **62a/b** (Scheme 11B).[70] Computational studies suggest that rhodacycle **63** is formed reversibly prior to the enantiodetermining alkyne carbometallation step. Similar non-enantioselective processes employing tethered alkenes and allenes have been reported.[71]



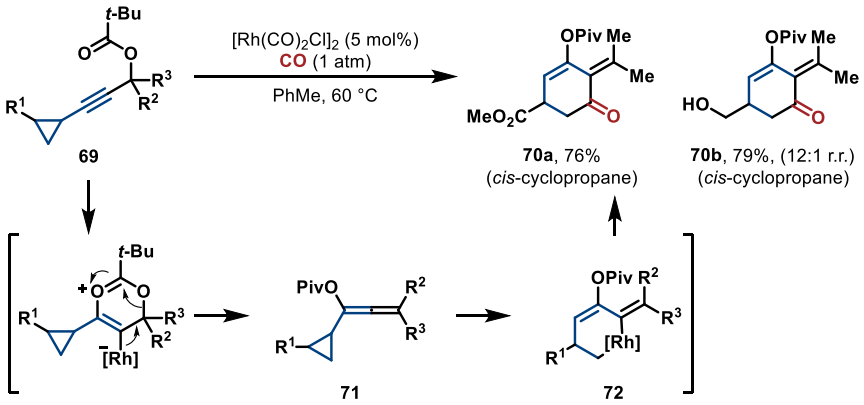
Scheme 11

The Yu group have also reported Rh(I)-catalysed carbonylative (3+1+2) cycloadditions of VCPs **64** to form 5,6- and 6,6-heterobicycles (e.g. **65a** and **65b**), where CO presumably inserts into a Rh(III)-allyl species (see **63** above) prior to carbometallation of the π-unsaturate (Scheme 12A).[71] Interestingly, subtle variation of the reaction solvent (i.e. 1,2-DCE instead of PhMe) and CO partial pressure resulted in a second equivalent of CO being incorporated into fused-tricycles **66a/b** (Scheme 12B).[72] Here, it is proposed that the vinyl moiety and CO inserts into rhodacycle **67** (instead of reductive elimination directly from **67**) to form rhodacycle **68** from which reductive elimination provides the observed tricyclic products. Yu and co-workers have also published protocols whereby the VCP serves as a five-carbon component,[73] which culminated in a carbonylative (5+2+1) cycloaddition applied to the total synthesis of hirsutic acid.[74]



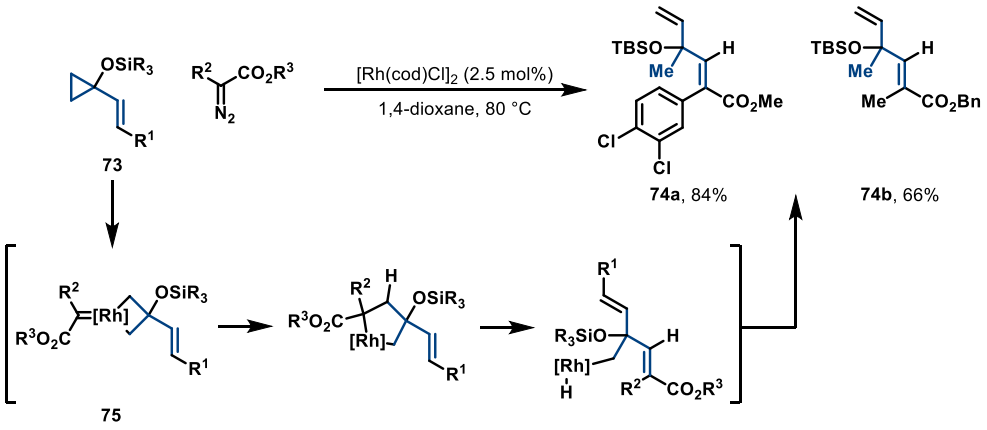
Scheme 12

Tang and co-workers have shown that allenylcyclopropanes (formed *in-situ* from propargylcyclopropanes **69**) can take part in C-C activation-based processes to form cyclohexenones **70a/b** (Scheme 13).[75] The transformation is initiated by the Rh(I)-mediated rearrangement of propargylcyclopropanes **69** to allenylcyclopropane **71**. Rh(I)-addition gives rhodacycle **72** from which carbonylation and reductive elimination give the observed products. Notably, the scope of this methodology extends to both *cis*- and *trans*-1,2-disubstituted cyclopropanes both of which proceed by cleavage of the less-substituted C-C bond of the cyclopropane. Another carbonylative cyclisation of allenylcyclopropanes has been applied to the formal synthesis of (-)-galanthamine.[76]



Scheme 13: Rh(I)-catalysed carbonylative (5+1) cyclisation of *in-situ* generated allenylcyclopropanes.

Recently, Wang and co-workers reported that Rh(I)-carbenes add to the distal C-C bond of siloxy-VCPs, which serves as a novel mode of C-C activation for this class of cyclopropane. As a result, highly substituted skipped dienes (e.g. **74a** and **74b**) could be accessed by the reaction of siloxy-VCPs **73** with Rh(I)-carbenes (Scheme 14). The transformation is proposed to begin with the formation of a Rh(I)-carbene which was shown to undergo oxidative addition to the distal C-C bond of VCPs **73** resulting in Rh(III)-intermediate **75**. 1,2-Migration into rhodacycle **75** is followed by β-hydride elimination and C-H reductive elimination in the formation of the observed products. The mechanism of the transformation was corroborated by stoichiometric and computational experiments.[77]

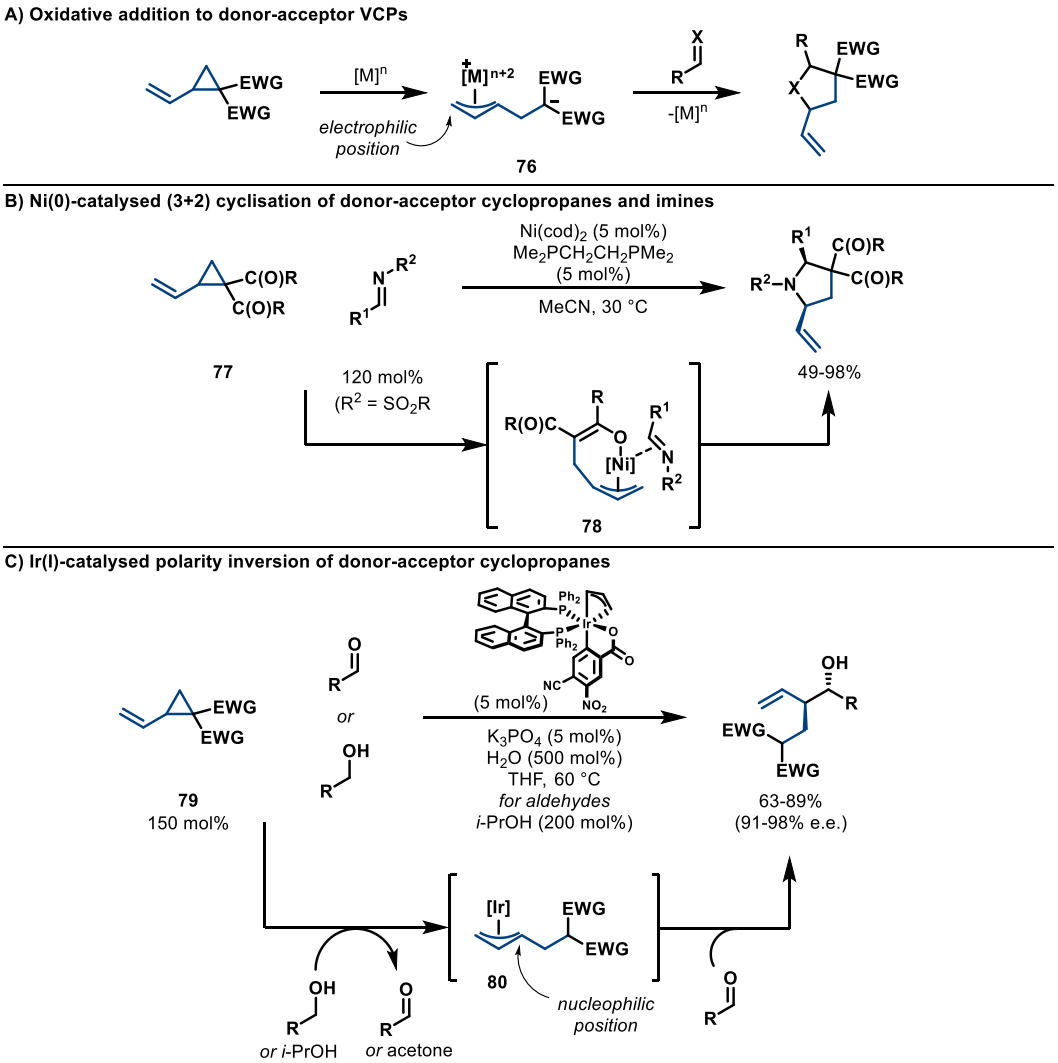


Scheme 14: C-C oxidative addition of a Rh(I)-carbene to siloxy-VCPs.

Donor-acceptor vinylcyclopropanes, where the cyclopropane is substituted by electron-withdrawing moieties, undergo S_N2-like oxidative addition by transition-metals (Scheme 15A). This forms acyclic intermediates **76**, which possess both an electrophilic metal-allyl moiety and a nucleophilic stabilised carbanion. The allyl-moiety of intermediates **76** can undergo reaction with nucleophiles (e.g. Grignard reagents), or polarised π-unsaturates (e.g. ketones, imines). Various Pd-, Fe- and Ni-catalysed examples of this process have been reported.[78-84] Matsubara and co-workers described a Ni(0)-catalysed (3+2) cycloaddition of donor-acceptor VCPs **77** with imines to form

pyrrolidines, which proceeded by a slightly different mechanism (Scheme 15B).[85] In this case, Ni(0)-addition is proposed to form Ni(II)-allyl complex **78** (instead of analogous acyclic intermediates **76**), which engaged imines to form pyrrolidines.

Krische and co-workers reported that, under Ir(I)-catalysed transfer hydrogenation conditions, donor-acceptor VCPs form *nucleophilic* π-allyl complexes **80** (Scheme 15C).[86] This polarity inversion of VCPs was demonstrated by the coupling of VCPs **79** with added or *in-situ* generated aldehydes to form homoallylic alcohols with high levels of diastereo- and enantiocontrol (91–98% e.e.). The reductant in this process is provided by the Ir(I)-mediated dehydrogenation of an alcohol, which generates a suitable aldehyde coupling partner in the transfer hydrogenation process. This strategy has been review recently,[87] and a similar Pd(0)-catalysed protocol has since been developed.[88]

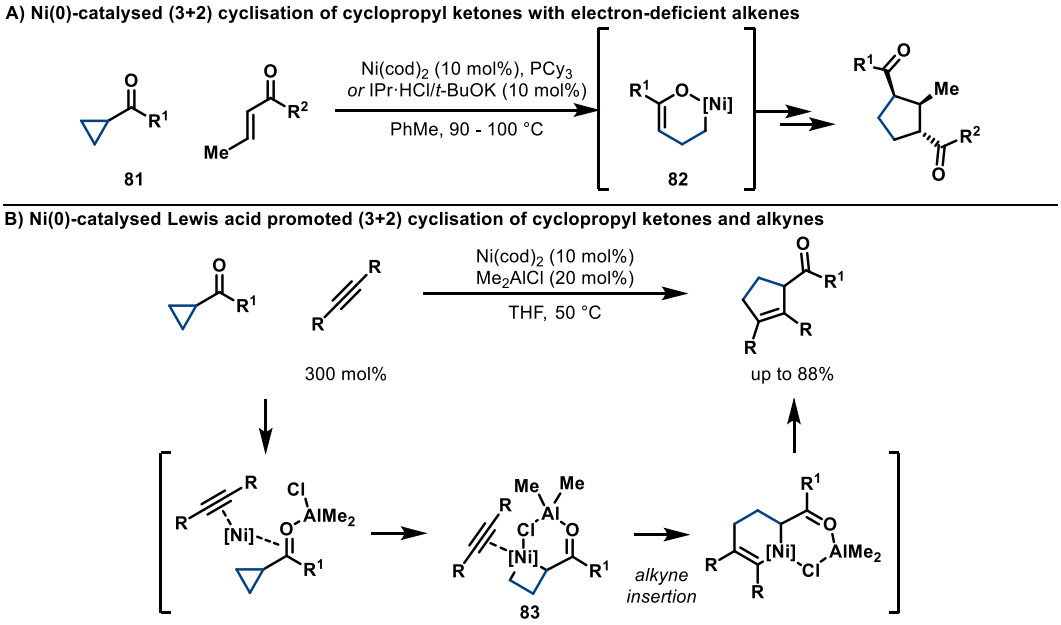


Scheme 15

1.2.1.4 Cyclopropyl ketone and imines

C-C oxidative addition to cyclopropanes with adjacent *polarised* unsaturation (e.g. cyclopropyl ketones and imines) is less well developed than for VCPs because electron-deficient cyclopropanes are less activated to metal addition. Nevertheless, several examples of C-C activation processes involving cyclopropyl ketones (or imines) are known, and these typically proceed by a similar mechanism to vinylcyclopropanes (see Scheme 10, A). This class of substrate is appealing in the context of C-C activation because substituted-analogues are often synthetically accessible in enantioenriched form.

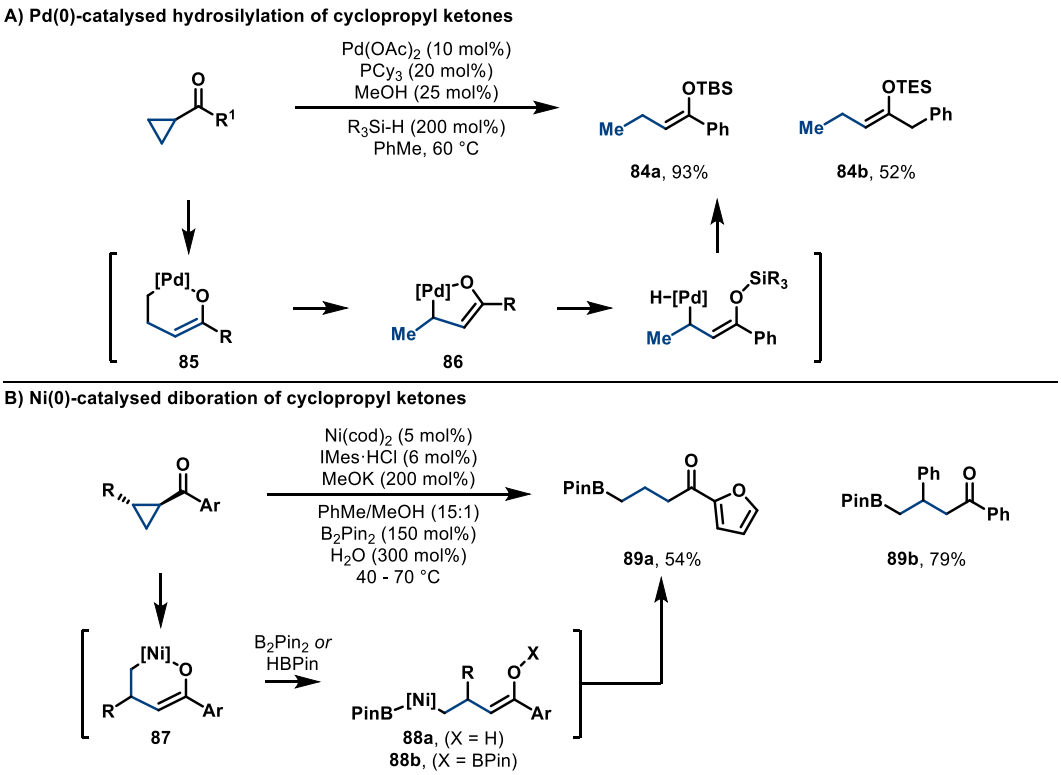
Liu, Montgomery and co-workers;[89-90] and Ogoshi and co-workers[91-93] have shown that under Ni(0)-catalysis, cyclopropyl ketones or imines can incorporate alkenes to provide functionalised cyclopentanes. For example, Ni(0)-activation of cyclopropylketones **81** provides nickelacycle **82** which reacts with polarised alkenes to form the observed cyclopentanes (Scheme 16A). In order to expand the methodology to include external alkynes, Ogoshi and co-workers employed the Lewis acid, Me_2AlCl, which facilitated the synthesis of cyclopentenes (Scheme 16B).[93] The mechanism of the Lewis acid-mediated coupling is proposed to begin with the formation of four-membered nickelacycle **83**. Stoichiometric experiments indicate that four-membered nickelacycle **83** is stabilised by a Ni-Cl interaction thus preventing isomerisation to a six-membered nickelacycle (cf. **82**). Migratory insertion of the external alkyne into nickelacyclobutane **83**, and reductive elimination affords cyclopentenes.



Scheme 16

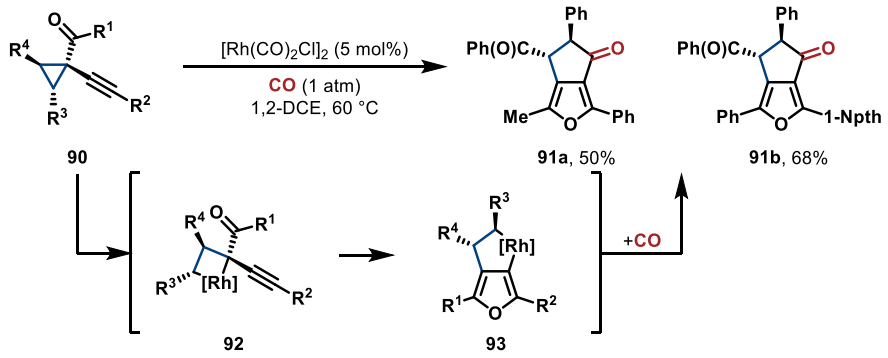
A Pd(0)-catalysed hydrosilylation of cyclopropyl ketones was developed by Oshima and co-workers, which provided access to (*Z*)-silyl enol ethers **84a/b** (Scheme 18A).[94] The mechanism of the transformation begins with the formation of six-membered palladacycle **85**, which isomerised to five-membered palladacycle **86** *via* consecutive β-hydride elimination and hydrometallation steps as

evidenced by deuterium labelling studies. Palladacycle **86** undergoes transmetallation with a tertiary silane and reductive elimination to give the observed products. In a related Ni(0)-catalysed reaction, cyclopropyl ketones react to form six-membered nickelacycles **87** which are trapped by B_2Pin_2 to form boryl enol ethers **88b**. Upon C-B reductive elimination and hydrolysis of the resulting boryl enol ethers, alkylboronic esters (e.g. **89a** and **89b**) are formed (Scheme 18B).[95] Ye and co-workers have since reported a related dual Ni/Al-catalysed enantioselective coupling of cyclopropylamides and alkynes.[96]



Scheme 18

Zhang and co-workers have also shown that propargylic cyclopropyl ketones **90** can be activated by a simple neutral Rh(I)-catalyst, under carbonylative conditions, to form furan-fused cyclopentanones (e.g. **91a** and **91b**) (Scheme 19).[97] The transformation is proposed to initiate by C-C oxidative addition to cyclopropylketone **90**. The resulting rhodacyclobutane **92** undergoes

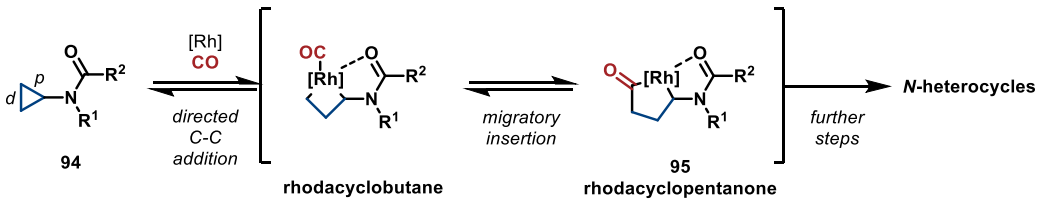


Scheme 19: Rh(I)-catalysed carbonylative rearrangement of alkynyl cyclopropyl ketones.

cycloisomerisation to rhodacycle **93**. This is followed by CO insertion and reductive elimination to give the furan-fused products.

1.2.1.5 Directed metal-addition to unactivated cyclopropanes

C-C activation of non-activated cyclopropanes is well-established but traditionally restricted to simple reduction and isomerisation processes.[16, 98] Application of this substrate class to complexity generating reactions is challenging because of the often low regioselectivity observed for metal addition to minimally differentiated C-C bonds and the poor stability of the resulting organometallic intermediates. Directed C-C oxidative addition processes can alleviate these issues. A directing-group strategy has been adopted at Bristol to facilitate the carbonylative formation of rhodacyclopentanones **95** from non-activated cyclopropane derivatives **94** (Scheme 20).[99-100] Rhodacyclopentanones generated in this way have been trapped by tethered π-unsaturates and nucleophiles providing access to structurally complex heterocyclic scaffolds.[99, 101-106] The development of this approach has been discussed and the resulting methodologies have been reviewed.[100, 107] An in-depth discussion of the carbonyl-directed carbonylative ring expansion strategy, developed at Bristol, will be presented in Section 1.3, and methodologies based around this process will be introduced at appropriate points throughout this thesis.

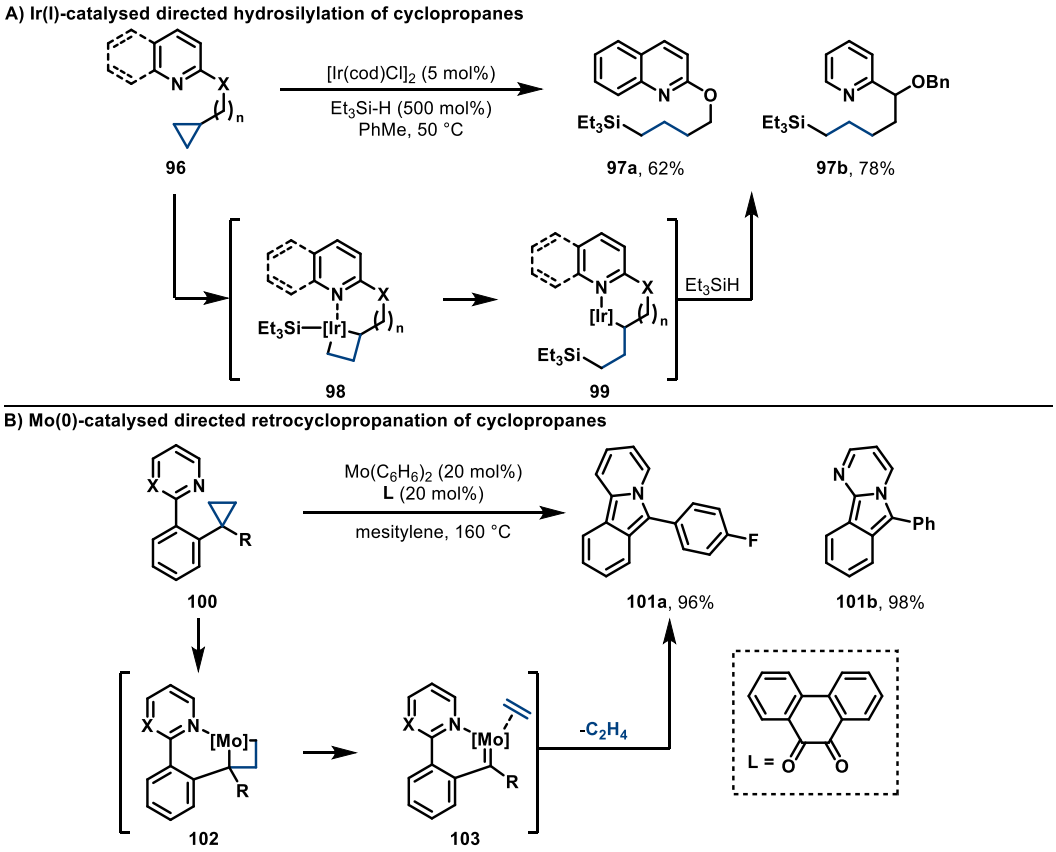


Scheme 20: Rh(I)-catalysed carbonylative ring expansion of aminocyclopropanes.

Recently, other examples of processes involving directed C-C addition processes of non-activated cyclopropanes have emerged. In 2017, Takai, Murai and co-workers published a pyridine-directed, Ir(I)-catalysed hydrosilylation of cyclopropanes **96** to form linear silanes (e.g. **97a** and **97b**) (Scheme 21A).[108] Control experiments provided evidence for the proposed mechanism. This begins with the formation of a Ir(I)-silane species, which is directed by the pyridine moiety to the proximal C-C bond of the cyclopropane to form iridacyclobutane **98**. Subsequent regioselective C-Si reductive elimination takes place to form six-membered Ir(I)-chelate **99** such that the pyridine-Ir bonding interaction is maintained. Reaction of Ir(I)-species **99** with a second equivalent of silane gives the product and regenerates the Ir(I)-silane catalyst.

In 2018, Asako, Takai and co-workers demonstrated the pyridine-directed Mo(0)-catalysed retrocyclopropanation of cyclopropylarenes **100** to form pyrido[2,1-*a*]isoindoles (e.g. **101a** and **101b**) (Scheme 21B).[109] The retrocyclopropanation reaction is proposed to initiate by pyridine-directed

Mo(0)-addition to the proximal C-C bond of the cyclopropane. The resulting four-membered Mo(II)-intermediate **102** undergoes a retro-(2+2)-cycloaddition to generate ethene and Mo-carbene species **103**, which is intercepted by the pyridyl group to form the observed products. Ethene generated in this process was observed by NMR studies, and computational studies support the proposed mechanism.



Scheme 21

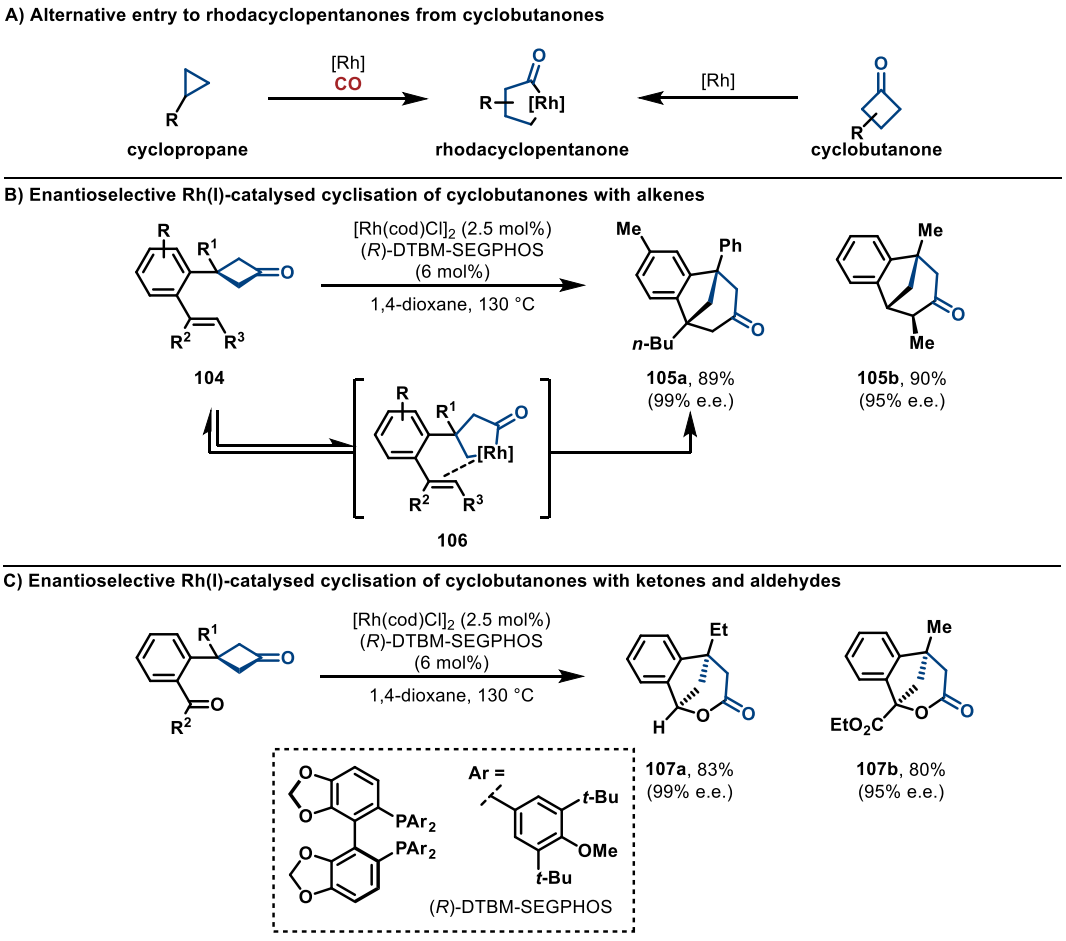
1.2.2 Cyclobutane-based processes

Cyclobutane-based rings possess significant ring strain, albeit typically less than cyclopropane-based rings, and the C-C bonds are less bent than in cyclopropanes (see Section 1.2).[18] As a result, C-C oxidative addition to cyclobutanes by transition metals is currently limited to highly strained analogues containing sp^2-centres, such as biphenylenes, and (benzo)cyclobutanones. Other cyclobutane-based rings undergo C-C cleavage *via* β-carbon elimination, but these examples are outside the scope of the current discussion.[15] Biphenylenes are among the most strained cyclobutane rings, and, as a result, have a rich history of transition metal-mediated C-C activation processes. However, the organometallic intermediates (and resulting products) formed in biphenylene-based processes are largely composed of sp^2-centres, so will not be discussed here in detail; several reviews are available which cover this topic.[15, 110]

1.2.2.1 Cyclobutanones

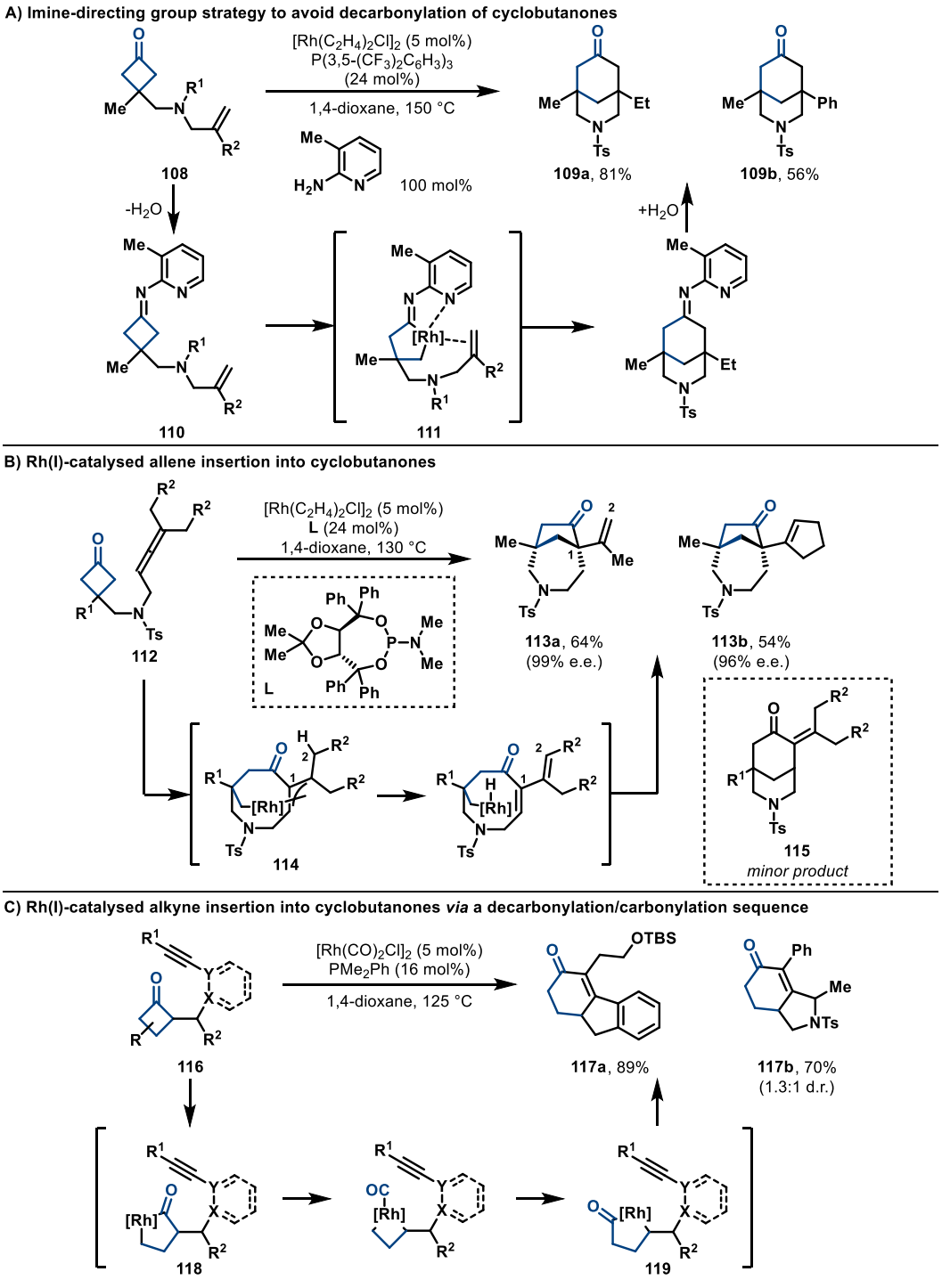
Seminal studies by Murakami and co-workers on Rh(I)-catalysed C-C oxidative addition to cyclobutanones showed that the catalyst added to the weaker acyl-C bond, which provided an alternative entry to rhodacyclopentanones (Scheme 22A).[111-112] Rhodacyclopentanones generated in this way have since been incorporated into several methodologies which have provided access to diverse heterocyclic compounds. The chemistry of rhodacyclopentanones has been recently reviewed.[113]

Building upon earlier work by Murakami and co-workers,[114] Cramer and co-workers achieved the enantioselective synthesis of benzo-fused bridged compounds (e.g. **105a** and **105b**) from cyclobutanones **104** using an (*R*)-DTBM-SEGPHOS-ligated Rh(I)-catalyst (Scheme 22B).[115-116] The transformation is proposed to begin with enantioselective Rh(I)-addition to the acyl-C bond of cyclobutanones **104** to form rhodacyclopentanones **106**. Alkene carbometallation is followed by reductive elimination to provide the observed products. Further developments allowed the insertion of ketones and aldehydes into analogous rhodacyclopentanones (not shown) allowing the enantioselective synthesis of bridged lactones (e.g. **107a** and **107b**) (Scheme 22C).[117] The successful application of an aldehyde in this process is notable because these are prone to C-H oxidative addition by Rh(I)-catalysts.



Scheme 22

Decarbonylation of rhodacyclopentanones is an often-encountered side-reaction of these processes. To avoid this, Ko and Dong[118] adapted the pyridyl-directed C-C activation strategy of Jun and Lee[119] to cyclobutanone-based processes. Here, cyclobutanones **108** are treated with a stoichiometric quantity of 2-amino-3-methylpyridine, which results in the *in-situ* formation of imine **110** (Scheme 23A). The imine-based directing group then directs Rh(I)-addition to provide Rh(III)-species **111**, from which CO extrusion cannot occur. Instead, Rh(III)-intermediate **111** is



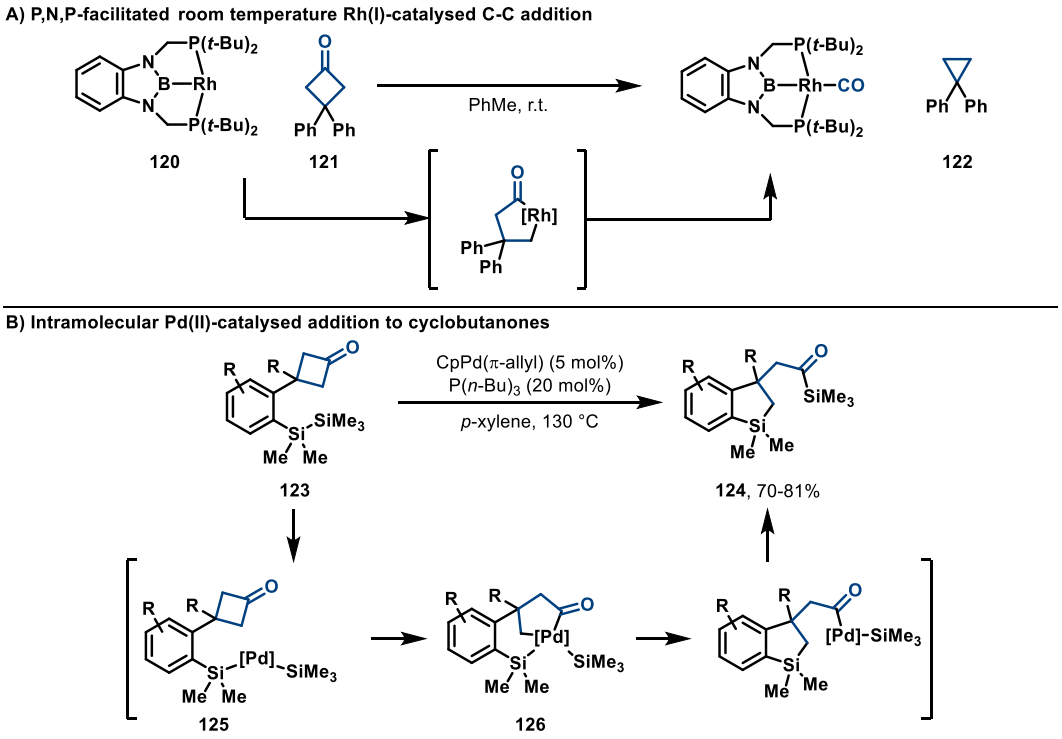
Scheme 23

intercepted by the tethered alkene to form bridged heterocyclic imines which are hydrolysed upon work-up to provide the ketone products (e.g. **109a** and **109b**).

A closely related process employed tethered allenes to intercept rhodacyclopentanones in the enantioselective synthesis of [4.2.1] bridged compounds without the use of an imine-directing group (Scheme 23B).[120] C-C oxidative addition of a TADDOL-phosphoramidite-ligated Rh(I)-catalyst into cyclobutanone **112** and allene-insertion formed Rh(III)-allyl intermediate **114**. β-Hydride elimination from C2, hydrometallation and reductive elimination took place to provide [4.2.1] bridged compounds (e.g. **113a** and **113b**) in preference to [3.3.1] products **115** (*via* C-C1 reductive elimination from **114**). Recently, rhodacyclopentanones generated from unsymmetrical cyclobutanones **116** were trapped by tethered alkynes to generate 5,6-enones (Scheme 23C).[121] The regioselectivity of the initial Rh(I)-addition step was investigated by ^{13}C-labelling studies, which indicated a preference for addition to the less-substituted acyl-C bond. The resulting rhodacyclopentanone **118** isomerises *via* a retrocarbonylation/carbonylation sequence to access the productive regioisomer **119**. Alkyne carbometallation and reductive elimination provided the observed products.

A significant restriction of most C-C oxidative addition methodologies is the requirement of high reaction temperatures (typically 90–150 °C). In what was a significant development in this respect, Murakami and co-workers presented the *P*,*N*,*P*-ligand-bound Rh(I)-catalyst **120** which catalysed the room temperature decarbonylation of cyclobutanone **121** to form cyclopropane **122** (Scheme 24A).[122] This advance suggests that the design of an optimised catalyst system for C-C oxidative addition to cyclobutanones might significantly improve these processes.

Whereas the majority of cyclobutane-based C-C activation processes are catalysed by Rh(I)-species, Murakami and co-workers reported a Pd(0)-catalysed transformation of cyclobutanones **123** into acylsilanes **124** (Scheme 24B).[123] Mechanistic studies imply that the transformation is initiated by Pd(0)-addition to the Si-Si bond of cyclobutanone **123** to form electron-rich Pd(II)-intermediate **125**. Then, *intramolecular* Pd(II)-addition to the cyclobutanone results in the formation of Pd(IV)-intermediate **126**, which undergoes consecutive C-Si/acyl-Si reductive eliminations to form acylsilanes **124**.



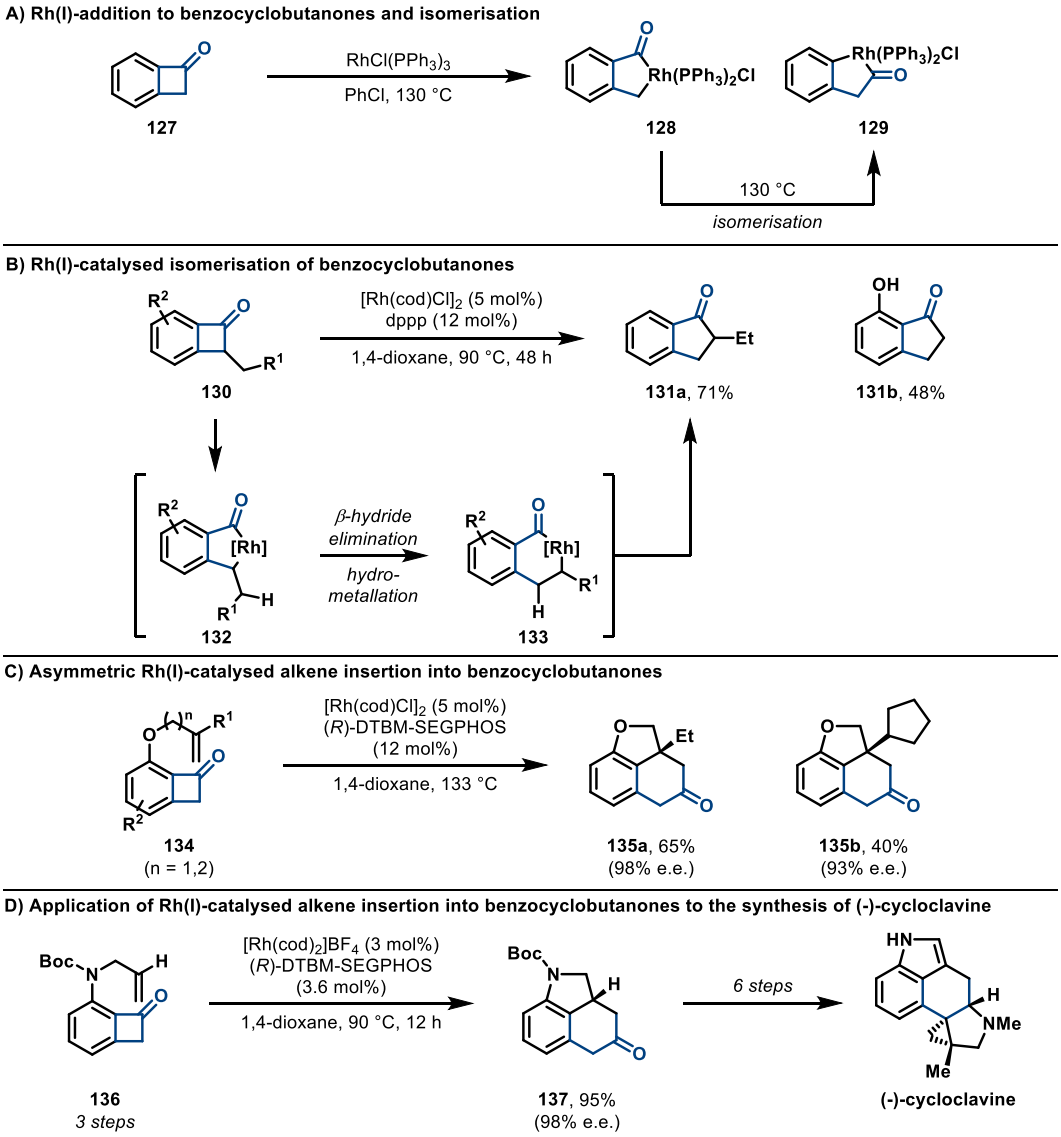
Scheme 24

1.2.2.2 Benzocyclobutanones

Benzocyclobutanones are another class of cyclobutanone that have been incorporated into C-C activation methodologies. The acyl-C(sp^3) and acyl-C(sp^2) bonds of the cyclobutanone ring are differentiated, which raises the possibility of forming one of two regioisomeric intermediates upon C-C oxidative addition. In 1992, Liebeskind showed that Wilkinson's catalyst preferentially inserted into the less-hindered C-C bond of benzocyclobutanone **127** to form rhodacyclopentanone **128**, which, upon heating, isomerised to the more stable regioisomer **129** (Scheme 25A).[124] Computational studies have since shown that isomerisation likely occurs by a retrocarbonylation/carbonylation sequence.[125] The Dong laboratory have exploited the rearrangement of benzocyclobutanone-derived rhodacyclopentanones for the development of several intramolecular cycloadditions. In early work, the C-C addition preference of a Rh(I)-catalyst was demonstrated in the isomerisation of simple benzocyclobutanones **130** to benzocyclopentanones (e.g. **131a** and **131b**) (Scheme 25B).[126] Here, Rh(I)-addition to the less substituted acyl-C(sp^3) bond of benzocyclobutanone **130** forms rhodacyclopentanone **132** from which β-hydride elimination and hydrometallation forms six-membered rhodacycle **133**. Reductive elimination then forms the observed indanones. Further evidence for this mechanism was later provided using computational methods.[127]

At higher reaction temperatures (>130 °C vs 90 °C), the initially formed rhodacyclopentanone (e.g. **128**) isomerises to the thermodynamically preferred regioisomer (e.g. **129**), which can then take part in further intramolecular transformations. This allowed benzocyclobutanones **134**, bearing tethered

alkenes, to undergo intramolecular cycloaddition to form tricyclic benzene derivatives (e.g. **135a** and **135b**) (Scheme 25C).[128-129] Since this early example, several groups have published related transformations in which various phenol, or aniline tethered π-unsaturates (including alkynes,[130] acrylamides,[131] ketones[132] and oximes[133]) are inserted into rhodacyclopentanones to form tricyclic compounds, often with enantiocontrol. Additionally, a Co(0)-catalysed process has been reported.[134]

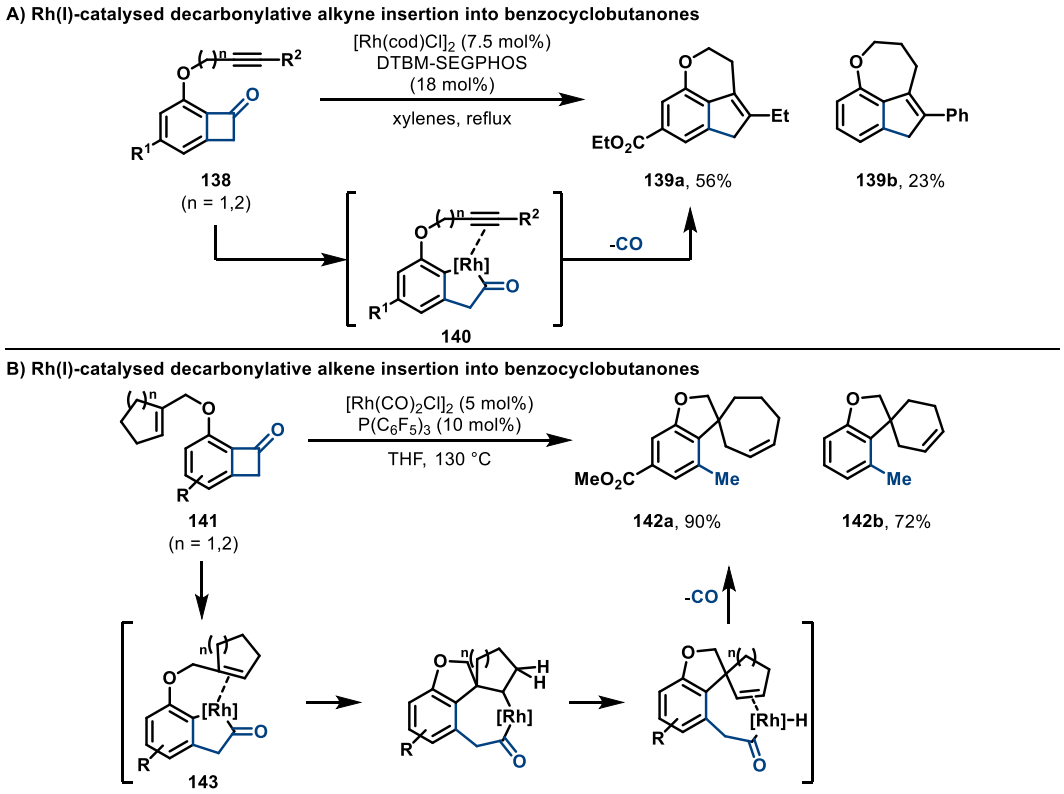


Scheme 25

Intramolecular trapping of benzocyclobutanone-derived rhodacyclopentanones by alkenes has been showcased in the total synthesis of several natural products, which is a testament to the maturity of these processes. For example, Dong and co-workers have recently disclosed the asymmetric total synthesis of (-)-cycloclavine and (-)-5-*epi*-cycloclavine, which is enabled by an asymmetric Rh(I)-catalysed cycloaddition of benzocyclobutanone **136** (Scheme 25D).[135] Benzocyclobutanone **136** was prepared in three steps and underwent a highly efficient and enantioselective Rh(I)-catalysed

intramolecular cycloaddition to form tricyclic compound **137** in 95% yield (98% e.e.). This compound was progressed in a diastereoselective manner to (-)-cycloclavine in a further six steps. The scope of the optimised Rh(I)-catalysed cycloaddition conditions was demonstrated to be broad.

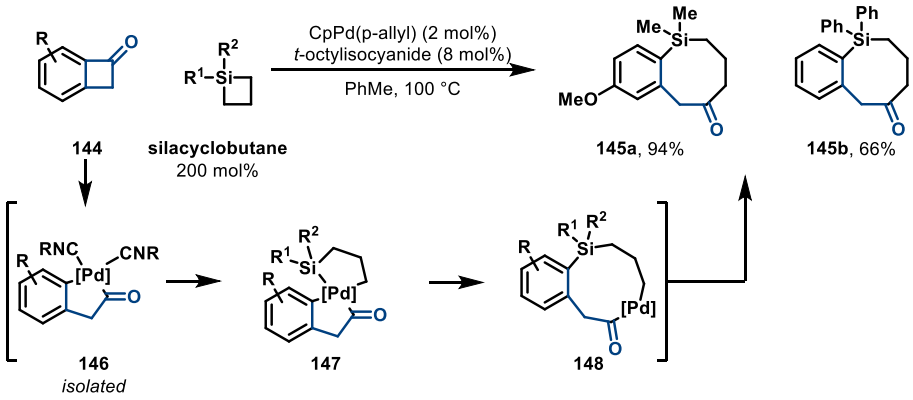
The Dong group have also demonstrated the feasibility of related decarbonylative processes. When benzocyclobutanones **138**, bearing tethered alkynes were treated with a DTBM-Segphos-ligated Rh(I)-catalyst, indanones (e.g. **139a** and **139b**) were formed (Scheme 26A).[130] Decarbonylation may take place from rhodacyclopentanone **140**, or from the intermediate resulting from migratory insertion of the alkyne. An alternative order of steps is also possible as was demonstrated by the decarbonylative synthesis of spiro-compounds (e.g. **142a** and **142b**) from benzocyclobutanones **141** containing tethered alkenes (Scheme 26B).[136] Here, incorporation of the alkene into rhodacyclopentanone **143** and β-hydride elimination occur prior to extrusion of CO and C-H reductive elimination to form the products.



Scheme 26

The majority of C-C activation processes involving benzocyclobutanones are catalysed by Rh(I)-complexes. However, Murakami and co-workers have recently described a Pd(0)-catalysed intermolecular cross metathesis of benzocyclobutanones **144** with silacyclobutanes to form benzofused eight-membered rings (e.g. **145a** and **145b**) (Scheme 27).[137] Optimisation studies identified *t*-octylisocyanide as a key additive; this led to the isolation of palladacyclopentanone **146**, which was then shown to be catalytically active. The proposed mechanism involves oxidative addition of

palladacycle **144** to a silacyclobutane, providing Pd(IV)-complex **147** from which Si-C reductive elimination gives Pd(II)-intermediate **148**. Acyl-C reductive elimination then provides the observed products. Later, the order of the catalytic steps was corroborated by computational methods.[138]

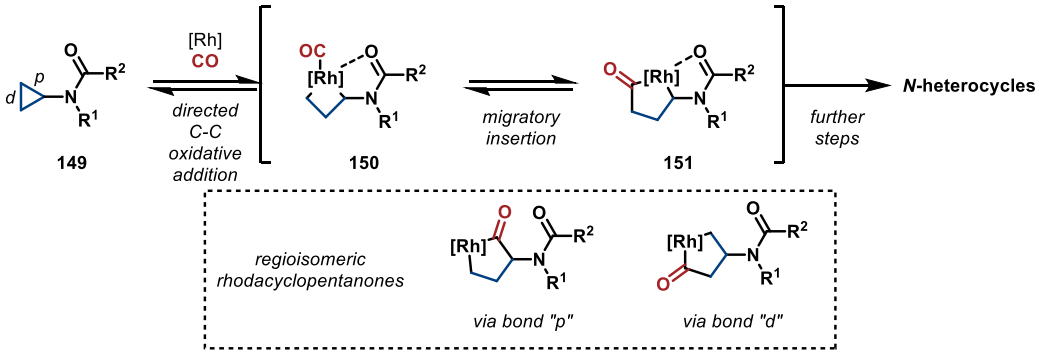


Scheme 27: Pd(0)-catalysed intermolecular cross-metathesis of benzocyclobutanones with silacyclobutanes.

The processes outlined in this introduction illustrate the diverse sp^3-rich structures that have been accessed using methodologies that employ oxidative addition of transition metal catalysts to C-C bonds of strained carbocycles. A particularly appealing application of these methodologies is their use for the synthesis of medium-sized ring systems. Indeed, the research contained within this thesis concerns the synthesis of various seven and eight-membered heterocycles *via* rhodacyclopentanones, which are generated from cyclopropanes by a strategy developed at Bristol. Key aspects of this strategy will now be presented as an introduction to the research contained in the following sections.

1.3 A directing group strategy for the generation of rhodacyclopentanones

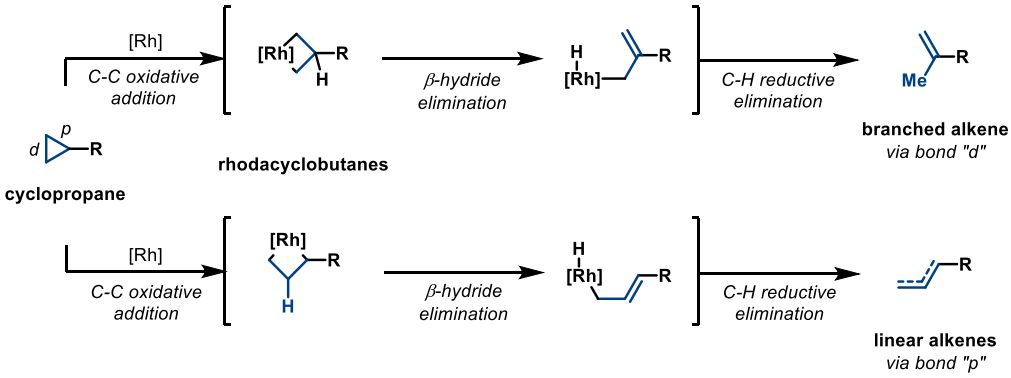
In 2013, former PhD student Dr Megan Shaw developed a strategy for the regioselective generation of rhodacyclopentanones from aminocyclopropanes.[99-100] The strategy employs a carbonyl-based directing group to promote regioselective oxidative addition of a Rh(I)-catalyst to the proximal C-C bond "*p*" of aminocyclopropanes **149** (Scheme 28). Migratory insertion of carbon monoxide into the resulting rhodacyclobutane **150** affords rhodacyclopentanones **151**, in which the Rh-O interaction is preserved. In this manner, a single rhodacyclopentanone can be generated out of three possible regioisomers (see the dashed box). Importantly, the steps leading up to rhodacyclopentanone formation (C-C oxidative addition and CO migratory insertion) have been shown to be reversible. Shaw and former PhD student, Dr Niall McCreanor, demonstrated the synthetic utility of these rhodacyclopentanones in the synthesis of complex *N*-heterocycles.



Scheme 28: Directing-group strategy for the generation of rhodacyclopentanones.

1.3.1 The importance of the directing group

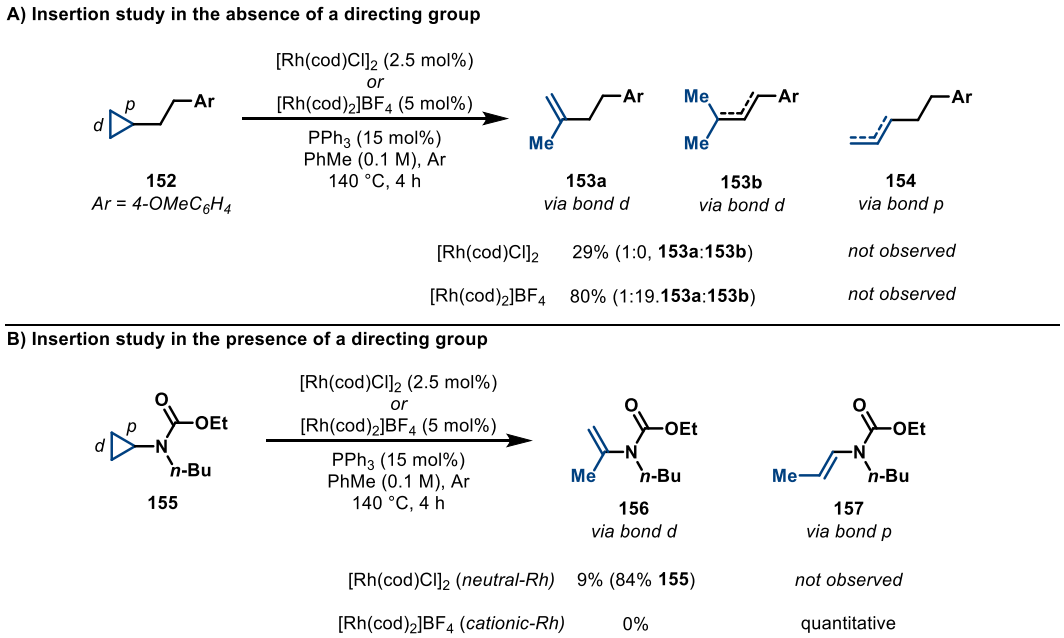
Key to the success of this strategy is the use of an appropriate combination of directing group and Rh(I)-catalyst. Initially, the role of the directing group was confirmed by carrying out an insertion experiment on cyclopropanes in the absence and presence of a directing group. An insertion experiment involves the reaction of a cyclopropane with a Rh(I)-catalyst under a non-carbonylative atmosphere (Scheme 29). Rhodacyclobutanes formed in this way are unstable and degrade *via* β-hydride elimination and C-H reductive elimination to form alkene products. The regiochemistry observed in the alkene products is an indication of the regiochemical preference of the Rh(I)-addition step: branched alkenes indicate addition to distal bond "*d*", whereas linear alkenes indicate addition to proximal bond "*p*".



Scheme 29: Insertion experiment to determine the site of metal addition to cyclopropanes.

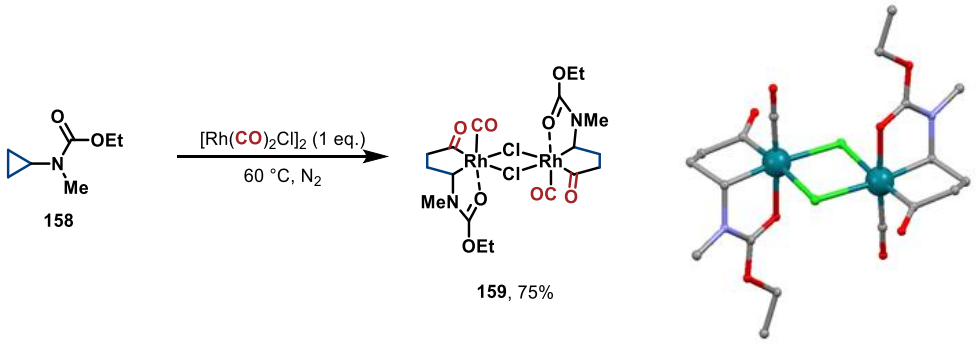
Shaw carried out insertion experiments with a cationic Rh(I)-catalyst on cyclopropane **152** (lacking a directing group) and aminocyclopropane **155** (bearing a carbamate directing group). Under these conditions, cyclopropane **152** reacted to form branched alkenes **153a** and **153b** exclusively, thus indicating Rh(I)-addition to the distal C-C bond "*d*" (Scheme 30A). In contrast, aminocyclopropane **155** reacted to form linear alkene **157** in quantitative yield *via* directed Rh(I)-addition to the proximal C-C bond "*p*" (Scheme 30B). Conversely, when aminocyclopropane **155** was treated with a *neutral* Rh(I)-catalyst, *branched* alkene **156** was the sole product. It was reasoned that the neutral Rh(I)-catalyst

is not sufficiently Lewis-acidic to be directed under non-carbonylative conditions. Shaw further demonstrated that other *N*-based directing groups are capable of directing Rh(I)-addition, including amides and sulfonamides.



Scheme 30

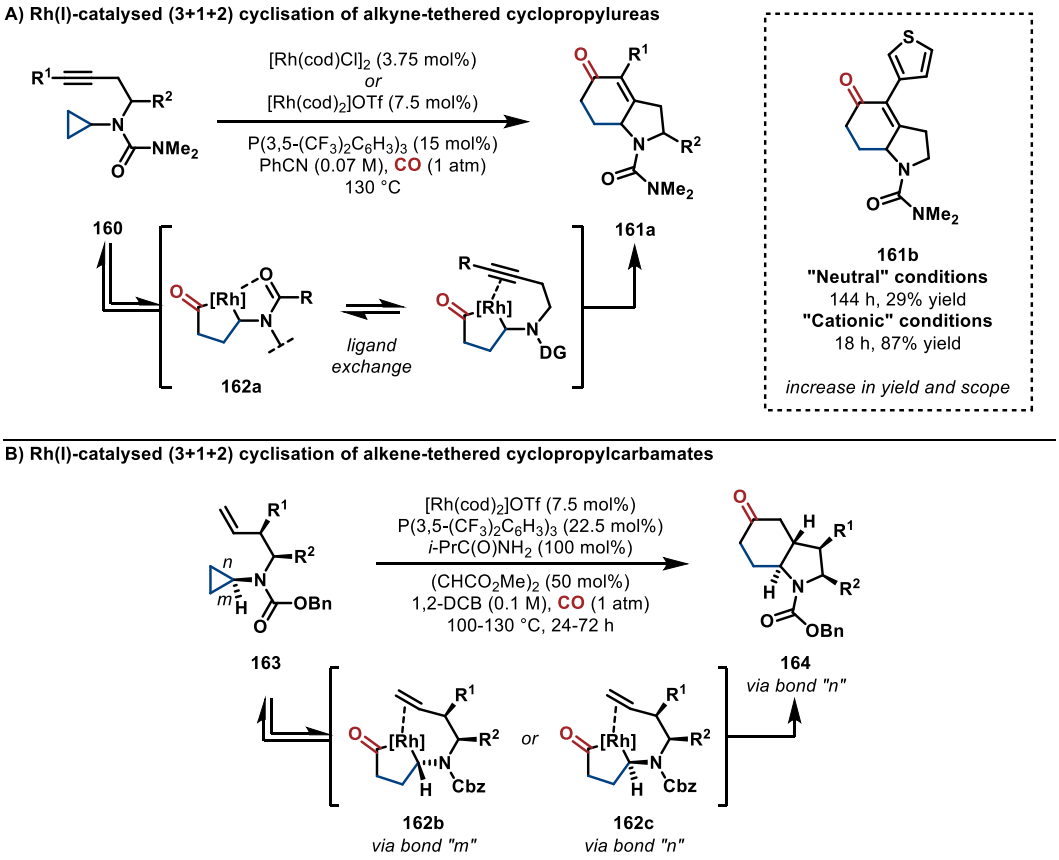
The insertion studies discussed above indicate the regioselectivity of Rh(I)-addition to cyclopropanes in the absence of carbon monoxide, but it was postulated that this preference might change under carbonylative conditions because the electron-withdrawing CO ligands would make the Rh(I)-catalyst more "cationic" in character. In order to probe this, a range of stable rhodacyclopentanones were synthesised by the reaction of $[Rh(CO)_2Cl]_2$ with aminocyclopropane-derivatives and characterised by NMR, IR and X-ray crystallography. For example, cyclopropylcarbamate **158** was reacted with a stoichiometric quantity of $[Rh(CO)_2Cl]_2$ to form rhodacyclopentanone **159** in 75% isolated yield (Scheme 31). The X-ray structure of complex **159** reveals the rhodacyclopentanone regioisomer resulting from directed Rh(I)-addition to the proximal cyclopropyl C-C bond. In addition, the Rh-O directing group interaction is maintained. Further complexes bearing different directing groups were synthesised and their CO stretching frequencies measured in order to determine the relative strength of carbonyl-based directing groups. The CO stretching frequencies indicate that directing group strength is proportional to the Lewis basicity of the carbonyl (i.e. directing group strength increases in the order amide (2046 cm^{-1}) < carbamate (2044 cm^{-1}) < urea (2023 cm^{-1})).



Scheme 31: X-ray crystal structure of a rhodacyclopentanone.

1.3.2 Rh(I)-catalysed (3+1+2) cycloadditions of cyclopropane derivatives

Next, Shaw demonstrated that rhodacyclopentanones generated by the directing group strategy could be incorporated into cycloaddition reactions. It was discovered that treatment of cyclopropylureas **160** with a neutral Rh(I)-catalyst under a carbonylative atmosphere resulted in a (3+1+2) cycloaddition to form heterobicyclic enones **161** (Scheme 32A). The proposed mechanism begins with the formation of rhodacyclopentanone **162** *via* urea-directed Rh(I)-addition to cyclopropylureas **160**. Directing group dissociation and alkyne coordination is followed by alkyne migratory insertion and reductive



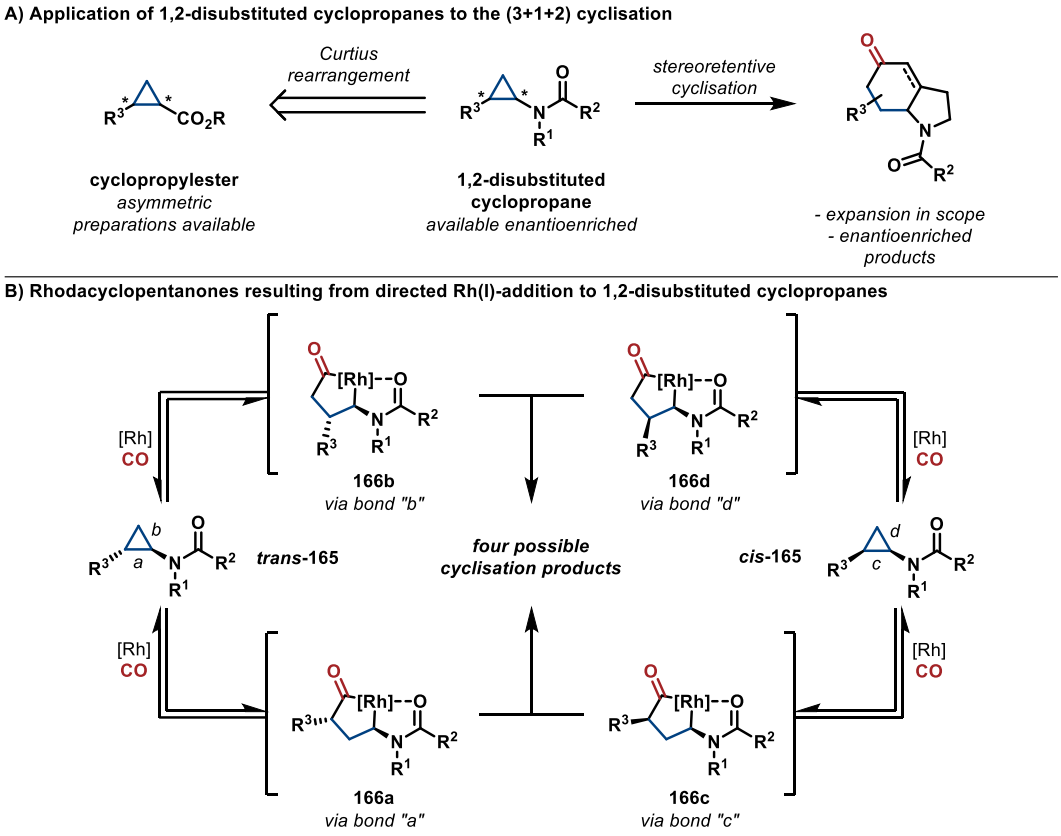
Scheme 32

elimination to provide the observed products. Optimisation of the reaction parameters revealed that a strongly coordinating urea directing group is required to outcompete the alkyne for coordination of the Rh(I)-catalyst. In this way, both the directed C-C addition and subsequent alkyne coordination steps are facilitated. The original "neutral" catalytic conditions require long reaction times (>72 h), which is proposed to be the result of inefficient coordination between the neutral Rh(I)-catalyst and the directing group. This problem was solved by employing a combination of a cationic Rh(I)-catalyst and the coordinating solvent, benzonitrile. The new "cationic" conditions afforded universally decreased reaction times (<48 h) and an improvement in the substrate scope, as exemplified by the improved yield for thiophene derivative **161b** (see Scheme 32, A).

In 2015, Shaw and McCreanor published a second protocol employing the directed formation of rhodacyclopentanones.[102] In this example, a cationic Rh(I)-catalyst mediates the (3+1+2) cycloaddition of cyclopropylcarbamates **163** with tethered alkenes to form bicyclic ketones **164** (Scheme 32B). Notably, the efficiency of the (3+1+2) cycloaddition was improved by the addition of dimethyl fumarate and *iso*-butyramide additives. The role of these additives is not clear, but it was proposed that dimethyl fumarate may act as an electron-deficient ligand. Importantly, high diastereoselectivity was achieved in this process under cationic conditions for substrates bearing substitution on the alkene tether (i.e. at R^1 or R^2). This selectivity arises from reversible Rh(I)-addition to the diastereotopic proximal C-C bonds of cyclopropylcarbamate **163** (i.e. "*m*" or "*n*") to form diastereomeric rhodacyclopentanones **162b** or **162c**, which undergo alkene insertion at different rates.

1.3.3 Directed Rh(I)-addition to 1,2-disubstituted cyclopropanes

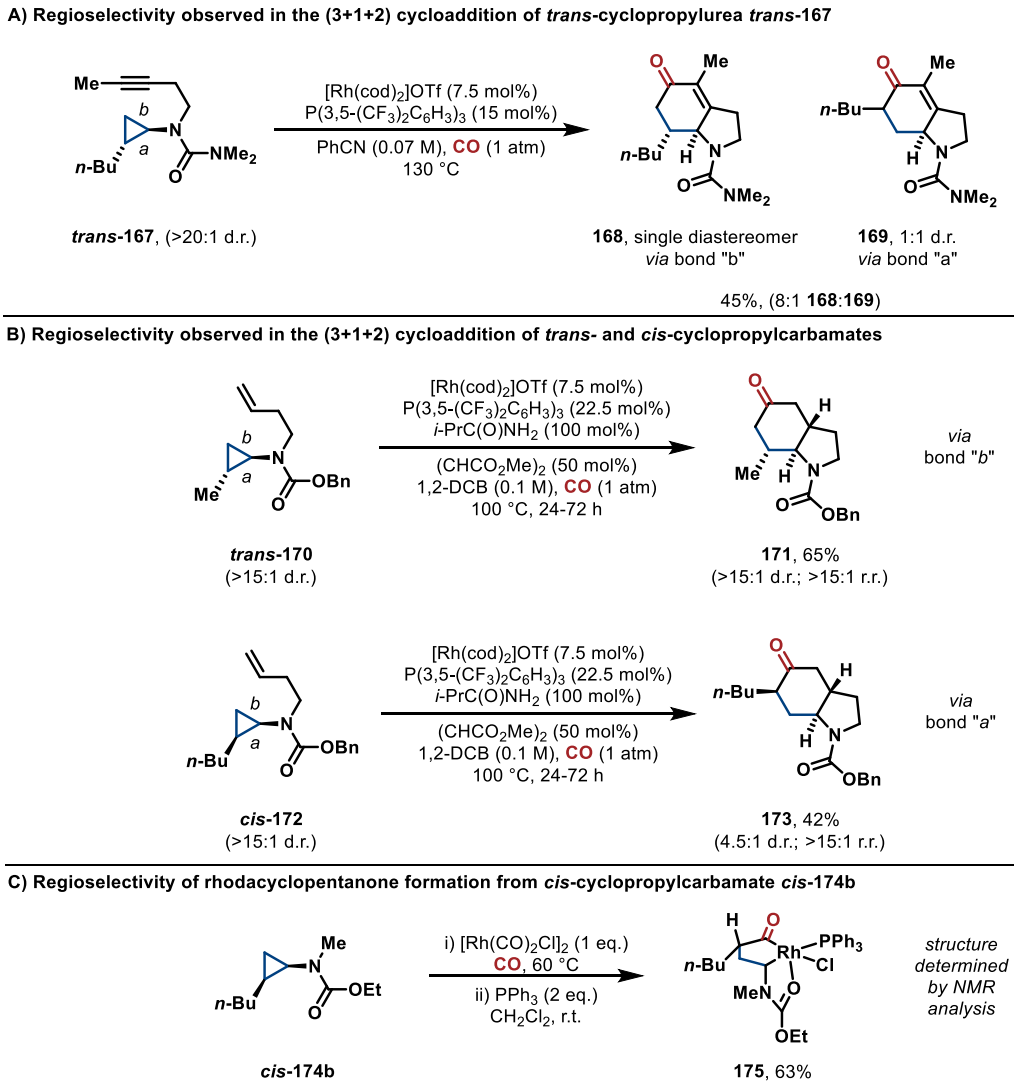
Application of 1,2-disubstituted cyclopropanes to C-C oxidative addition-based processes is desirable because they provide access to more highly substituted cycloadducts (Scheme 33A). Additionally, substituted cyclopropanes are often available in an enantioenriched form, potentially giving access to enantioenriched cycloadducts.[139-141] However, additional substitution on the cyclopropane ring introduces complications regarding the regioselectivity of C-C oxidative addition. For example, 1,2-disubstituted cyclopropanes can exist as either *trans*- or *cis*-diastereomers (see ***trans*-165** and ***cis*-165**) where each of the four proximal C-C bonds (i.e. "*a*" vs "*b*" vs "*c*" vs "*d*") are sterically and electronically differentiated (Scheme 33B). Consequently, directed C-C oxidative addition by a Rh(I)-catalyst to these cyclopropanes could give rise to four isomeric rhodacyclopentanones **166a-d**, and therefore four diastereomeric cycloadducts. The product formed by reaction of a 1,2-disubstituted cyclopropane therefore depends on the stereochemistry of the cyclopropane starting material (*trans*- or *cis*-), and the regioselectivity of the Rh(I)-addition step.



Scheme 33

Shaw and McCreanor investigated 1,2-disubstituted cyclopropanes in (3+1+2) cycloadditions in order to investigate the regioselectivity of the Rh(I)-addition step. When *trans*-substituted cyclopropane ***trans*-167** was subjected to the "cationic" conditions, enone **168** was formed (45% yield, 8:1 r.r.) as a result of Rh(I)-addition to the less sterically hindered C-C bond "*b*" (Scheme 34A). Notably (3+1+2) cycloaddition of ***trans*-167** proceeded with complete retention of the cyclopropane stereocentres, providing enone **168** as a single diastereomer. Similarly, *trans*-cyclopropylcarbamate ***trans*-170** reacted *via* Rh(I)-addition to the less-hindered bond "*b*" giving ketone **171** (65% yield) with complete stereoretention and regiocontrol (Scheme 34B). Conversely, *cis*-substituted cyclopropane ***cis*-172** provided cycloadduct **173** (42% yield, 4.5:1 d.r., >15:1 r.r.) *via* Rh(I)-addition to the *more* substituted C-C bond "*a*". It was proposed that the contrasteric regioselectivity observed for *cis*-substituted cyclopropane **172** was a result of the more electron-rich C-C bond "*a*" outcompeting bond "*b*" for initial coordination to the Rh(I)-catalyst, and therefore undergoing preferential oxidative addition. A similar effect has been observed whereby *cis*-alkenes coordinated more strongly to Rh(I)-organometallics than *trans*-alkenes.[142] The same regioselectivity for Rh(I)-addition to the more hindered bond "*a*" of *cis*-substituted cyclopropanes was observed in the formation of rhodacyclopentanone **175** from the stoichiometric reaction of *cis*-substituted cyclopropane ***cis*-174b** (Scheme 34C). The structure of rhodacyclopentanone **175** was determined by detailed NMR studies. These studies on the regioselectivity of Rh(I)-addition to substituted cyclopropanes demonstrate that

both product regioisomers can be accessed selectively by utilising either the *trans*- or *cis*-diastereomer of the substrate.



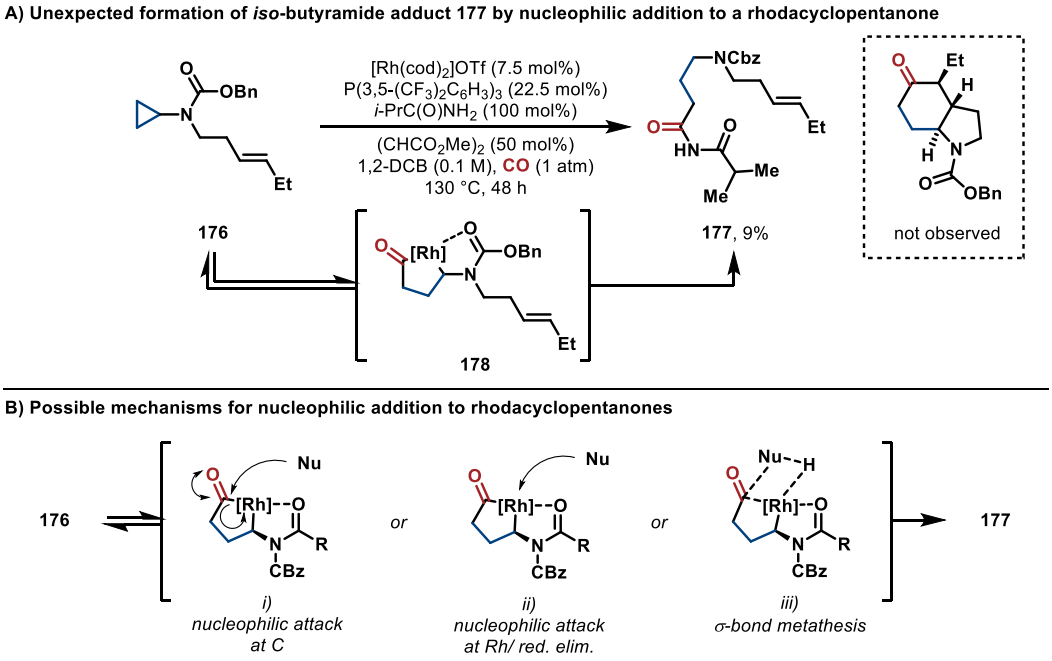
Scheme 34

1.4 Nucleophilic addition to rhodacyclopentanones

1.4.1 Intermolecular nucleophilic addition to rhodacyclopentanones

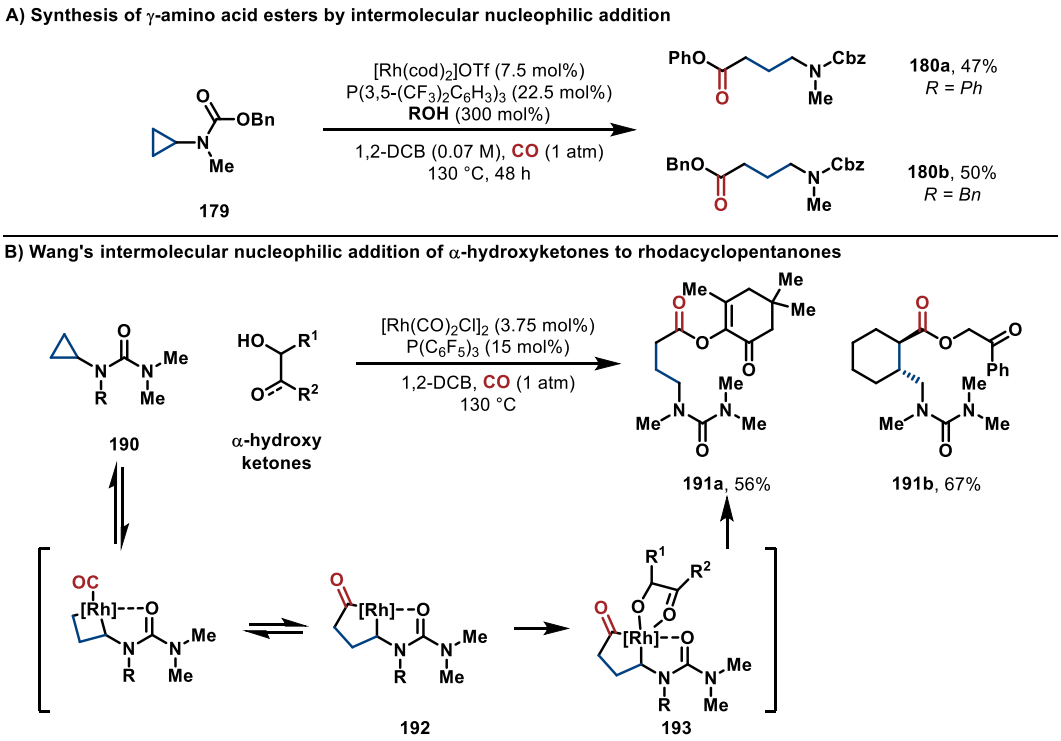
During investigations into the (3+1+2) cycloaddition of cyclopropylcarbamate **176**, McCreanor isolated carbonylation product **177** resulting from nucleophilic addition of *iso*-butyramide to rhodacyclopentanone **178** (Scheme 35A). Nucleophilic addition to a rhodacyclopentanone can foreseeably have occurred by one of three mechanisms: *i*) nucleophilic addition to the rhodacyclopentanone carbonyl, *ii*) nucleophilic addition to the Rh(III)-centre or *iii*) σ-bond metathesis (Scheme 35B). Murakami and co-workers had previously reported that rhodacyclopentanones can

undergo *intra*molecular nucleophilic addition of phenolic oxygen nucleophiles.[143] Nevertheless, the formation of adduct **177** serves as the first example of intermolecular nucleophilic addition to a rhodacyclopentanone. The novelty of this process prompted McCreanor to investigate the intermolecular process further.



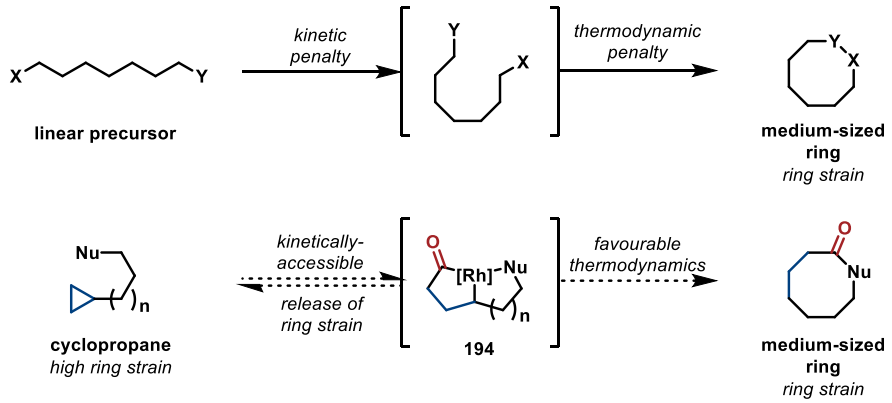
Scheme 35

Initial investigations involved nucleophilic addition to the rhodacyclopentanone generated from cyclopropylcarbamate **179** under cationic conditions (Scheme 36A). It was discovered that phenol and benzyl alcohol are effective nucleophiles, which lead to the formation of γ-amino acid ester derivatives **180a** and **180b** in moderate yields. γ-Amino acids are important biologically active chemical motifs however these can be synthesised readily.[144-145] Recently, Wang and co-workers published a related protocol involving intermolecular nucleophilic addition of α-hydroxy ketones to rhodacyclopentanones to form γ-amino acid esters (e.g. **191a** and **191b**) (Scheme 36B).[146] Here, rhodacyclopentanone **192** is formed by directed Rh(I)-addition to cyclopropylureas **190**. Then, a chelating nucleophile is required to aid coordination to the rhodacyclopentanone **192** resulting in the formation of intermediate **193** from which reductive elimination and protodemetallation provides the observed products. Due to the limited synthetic value of an intermolecular protocol for nucleophilic addition to rhodacyclopentanones, McCreanor's focus shifted to the development of an *intra*molecular cyclisation because it was recognised that this might be well suited to the synthesis of valuable medium-sized rings.



Scheme 36

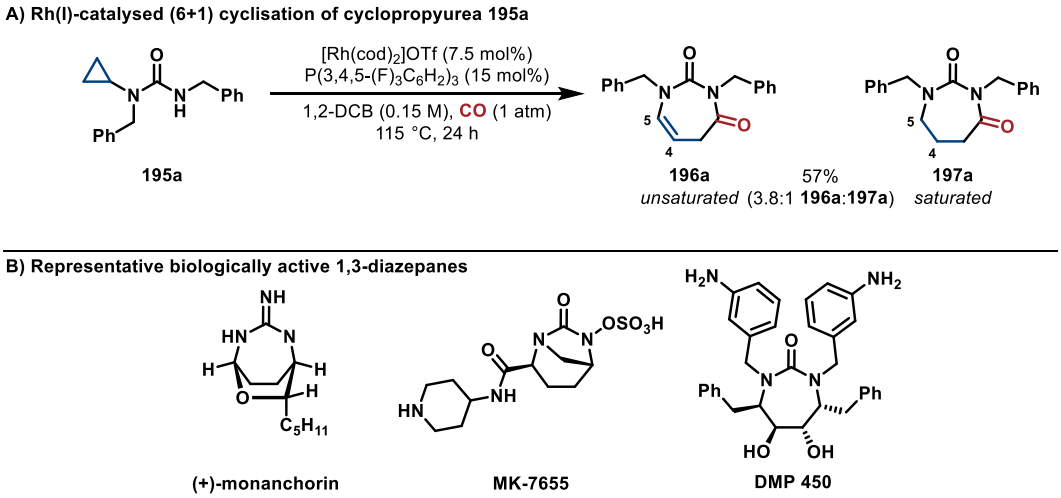
Medium-sized rings (8–11 membered rings) are typically more difficult to synthesise than five or six-membered rings because of additional kinetic and thermodynamic barriers to cyclisation. For example, it is kinetically unfavourable to bring two ends of a linear cyclisation precursor together in order to react, and this becomes less favourable as the length of the cyclisation precursor increases (Scheme 37).[147] Additionally, medium-sized rings are more strained than five or six-membered rings, thus resulting in a greater thermodynamic barrier to cyclisation.[148] The proposed strategy for the synthesis of medium-sized rings *via* intramolecular nucleophilic addition to rhodacyclopentanones would mitigate both of these barriers to cyclisation. The kinetic barrier to cyclisation would be reduced through the formation of a kinetically accessible 5,5-bicyclic intermediate **194** by intramolecular nucleophilic addition to a rhodacyclopentanone. Additionally, the thermodynamic penalty for forming a strained medium-sized ring is offset by the cleavage of a highly strained cyclopropane-based substrate.



Scheme 37: Strategy for the synthesis of medium-sized rings *via* kinetically accessible intermediates.

1.4.2 Intramolecular nucleophilic addition to rhodacyclopentanones: (6+1) carbonylative cyclisation of cyclopropylureas

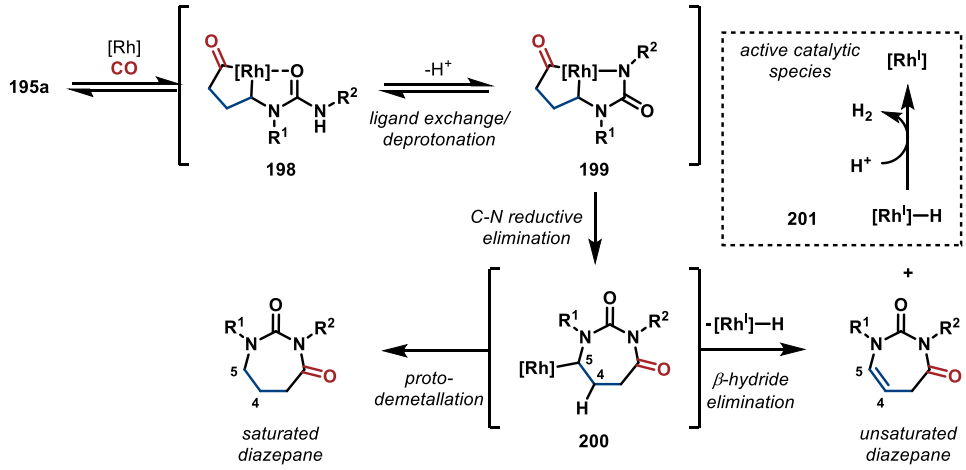
In order to investigate the strategy outlined in Scheme 37, McCreanor synthesised a selection of aminocyclopropanes bearing directing groups and tethered *O*- or *N*-nucleophiles, and subjected them to Rh(I)-catalysis under a CO atmosphere (more details are provided in Section 2.2.1). It was discovered that cyclopropylurea **195a** underwent Rh(I)-catalysed carbonylative (6+1) carbonylative cyclisation to form seven membered diazepanes **196a** and **197a** (57%, 3.8:1 **196a**:**197a**) which differ by the oxidation level of the C4-C5 position (Scheme 38A). 1,3-Diazepanes are important heterocycles, which are found in biologically active compounds including the potent HIV-integrase inhibitor, DMP 450,[149] the β-lactamase inhibitor, MK-7655,[150] and the natural mast cell inhibitor, (+)-monanchorin[151] (Scheme 38B).



Scheme 38

The mechanism of the (6+1) carbonylative cyclisation is proposed to proceed by urea-directed formation of rhodacyclopentanone **198** (Scheme 39). Ligand exchange of the carbonyl for the *N*-nucleophile and deprotonation provides intermediate **199**. C-N Reductive elimination then forms

diazepane **200**, which can either undergo protodemetallation to form saturated diazepanes, or β-hydride elimination to form unsaturated diazepanes. β-Hydride elimination from diazepane **200** forms a Rh(I)-hydride **201**, from which the active catalyst is regenerated by oxidative protonation and reductive elimination of dihydrogen (see the dashed box). Rh(III)-dihydrides have previously been reported to reductively eliminate dihydrogen.[143, 152]



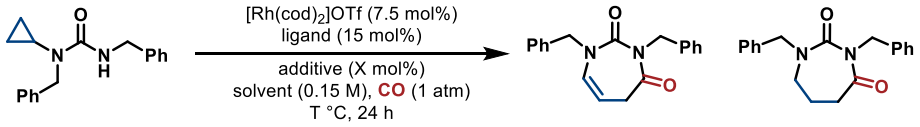
Scheme 39: Proposed mechanism for the (6+1) carbonylative cyclisation and regeneration of the Rh(I)-catalyst.

1.4.2.1 Optimisation of the (6+1) carbonylative cyclisation of cyclopropylureas

Optimisation studies were directed at improving the yield and selectivity of the reaction, and selected results are shown in Table 1. The discovery conditions formed unsaturated diazepane **196a** in 57% yield with poor selectivity (3.8:1, **196a**:**197a**) over the saturated diazepane **197a** (Entry 1). Initially, it was confirmed that cationic Rh(I)-catalysts are superior to neutral Rh(I)-catalysts. A significant improvement was achieved by employing PPh_3 as the ligand, which provided unsaturated diazepane **196a** in 90% yield but with only moderate selectivity (9:1, **196a**:**197a**) over the saturated product (Entry 2). The oxidation level selectivity could be greatly improved (85%, 25:1, **196a**:**197a**) by lowering the reaction temperature (Entry 3). The non-coordinating solvent 1,2-DCB was found to be the optimal solvent, with coordinating solvents such as benzonitrile affording the desired cycloadduct in diminished yield (Entry 4).

At this point, the optimal conditions for the (6+1) carbonylative cyclisation afforded excellent selectivity for unsaturated diazepane **196a**. An attempt was made to develop complimentary conditions for the formation of saturated diazepane **197a** to allow oxidation level divergent access to either diazepane. Several protic and hydridic additives were tested in order to promote protodemetallation from intermediate **200** (see Scheme 39), but selectivity in favour of the unsaturated diazepane **196a** remained (Entries 5-7). However, during these studies it was discovered that a substoichiometric quantity of benzoic acid (10 mol%) improved the yield of the unsaturated diazepane (Entry 8). Interestingly, by lowering the partial pressure of CO and employing the electron-deficient ligand

$P(3,4,5\text{-}(F)_3C_6H_2)_3$, the selectivity of the process could be reversed (37%, 1:2, **196a**:**197a**) in favour of the saturated diazepane **197a**, albeit with a significant decrease in overall yield (Entries 9 and 10). McCreanor's optimised conditions for the formation of unsaturated diazepane **196a** were used to investigate the scope of the reaction.



195a → **196a** *unsaturated* / **197a** *saturated*

Entry	Ligand	Additive	Solvent	T	Yield[a] (196a:196b)
1	$P(3,4,5\text{-}(F)_3C_6H_2)_3$	-	1,2-DCB	115 °C	57% (3.8:1)
2	PPh_3	-	1,2-DCB	115 °C	90% (9:1)
3	PPh_3	-	1,2-DCB	100 °C	85% (27:1)
4	PPh_3	-	PhCN	100 °C	53% (13:1)
5	PPh_3	CO/H_2 (1:1)	1,2-DCB	100 °C	95% (23:1)
6	PPh_3	sodium formate (200 mol%)	1,2-DCB	100 °C	-
7	PPh_3	H_2O (200 mol%)	1,2-DCB	100 °C	74% (24:1)
8	**PPh_3**	**$PhCO_2H$ (10 mol%)**	**1,2-DCB**	**100 °C**	**96% (15:1)**
9	$P(3,4,5\text{-}(F)_3C_6H_2)_3$	CO/N_2 (1:4)	1,2-DCB	130 °C	37% (1:2)
10	$P(3,4,5\text{-}(F)_3C_6H_2)_3$	CO/N_2 (1:1)	1,2-DCB	130 °C	66% (2.7:1)

[a] *In-situ* yield measured against an internal standard.

Table 1: Selected results from McCreanor's optimisation of the (6+1) carbonylative cyclisation of trisubstituted cyclopropylurea **195a**.

1.4.2.2 Scope of the (6+1) carbonylative cyclisation of cyclopropylureas

McCreanor synthesised a variety of cyclopropylureas (details in Section 2.1.2.1) to investigate the scope of the (6+1) carbonylative cyclisation, and the results are displayed in Table 2. Primary alkyl and aryl substitution was tolerated at R^1 as demonstrated by the formation of diazepanes **196b** and **196c** in 78% and 48% yield, respectively. Interestingly, reaction of *N,N'*-disubstituted urea **202a** (R^1 = H) formed the *saturated* diazepane **204a** selectively (1:6, **203a**:**204a**) in a combined yield of 63%; the implications of this result will be discussed further in Section 2.1.2.3. Substitution of the nucleophilic nitrogen (R^2) was less well tolerated except for simple alkyl substituted cyclopropylurea **195d**, which formed diazepane **196d** in 94% yield. Aryl and secondary alkyl substituents at R^2 performed poorly generating the corresponding diazepanes **196e-g** in low yield (14–39% yield). Finally, *N,N*-disubstituted urea **195h** (R^2 = H) formed the corresponding diazepane **196h** in only 22% yield.

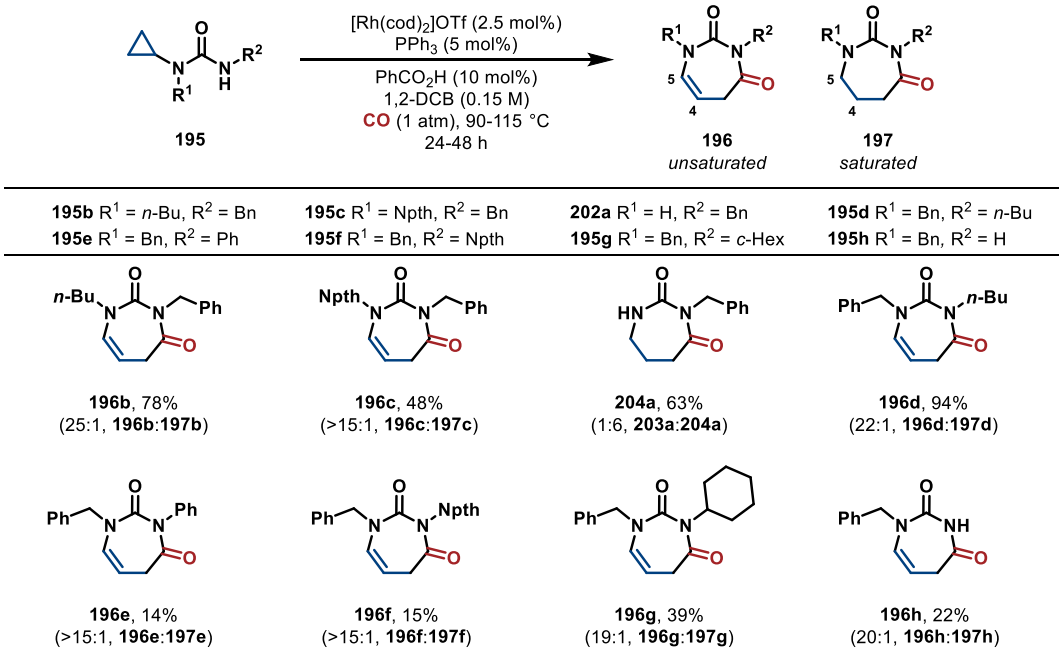
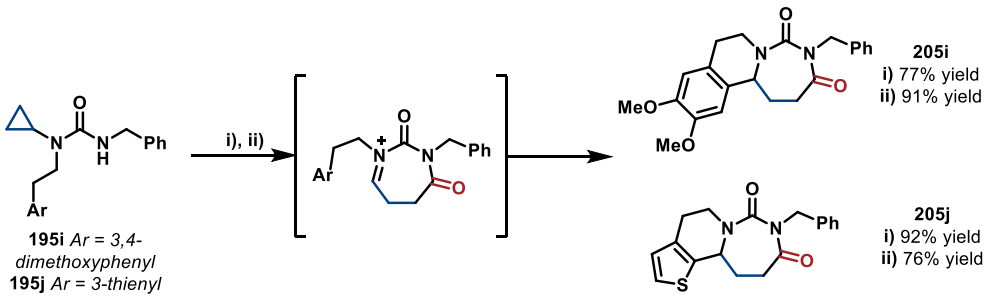


Table 2: Scope of McCreanor's conditions for the (6+1) carbonylative cyclisation of cyclopropylureas.

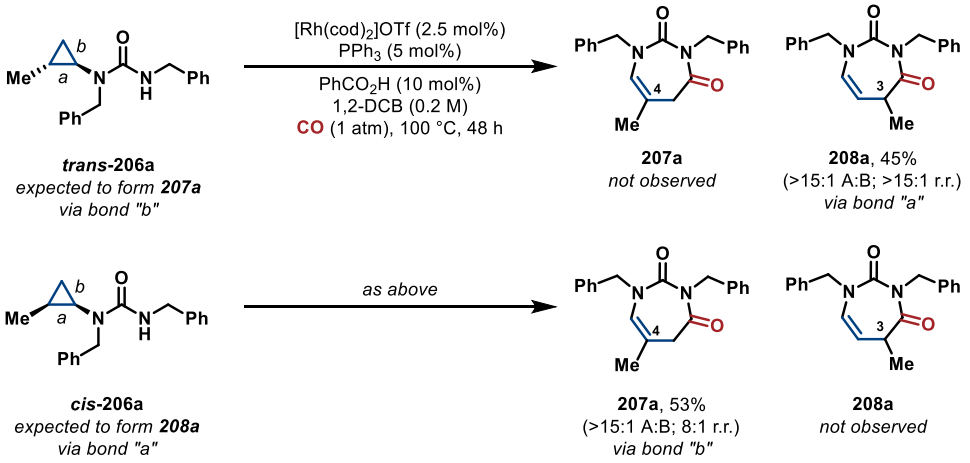
McCreanor demonstrated the reactivity of the enelactam moiety of unsaturated diazepanes by carrying out a Pictet-Spengler-like cyclisation (Scheme 40). Ureas **195i** and **195j**, which possess tethered electron rich aromatics, underwent high yielding (6+1) carbonylative cyclisations to form the corresponding diazepanes (not shown) **196i** (77%) and **196j** (92%), respectively. Upon treatment with TFA, the enelactam functionality was protonated, allowing Pictet-Spengler-like cyclisation to form tricyclic compounds **205i** and **205j** in 91% and 76% yield, respectively.



Scheme 40: Pictet-Spengler cyclisation of unsaturated diazepanes to give tricyclic products. Regents and conditions: i) $[Rh(cod)_2]OTf$ (2.5 mol%), PPh_3 (5 mol%), CO (1 atm), $PhCO_2H$, 1,2-DCB (0.2 M), 100 °C; ii) TFA (1000 mol%), CH_2Cl_2 (0.1 M), 60 °C.

McCreanor began to investigate the scope of the reaction with respect to both *cis*- and *trans*-1,2-disubstituted cyclopropanes. Based on previous work in Bristol (see Section 1.3.3), *trans*-cyclopropane ***trans*-206a** was expected to form C4-substituted diazepane **207a** by Rh(I)-addition to the less hindered C-C bond "*b*" (Scheme 41). Unexpectedly, ***trans*-206a** reacted *via* C-C bond "*a*" to form C3-substituted diazepane **208a** in 45% yield and as a single regioisomer with complete selectivity over

the saturated product. Also unexpectedly, *cis*-substituted cyclopropane ***cis*-206a** reacted *via* less hindered C-C bond "*b*" resulting in the selective formation of C4-substituted diazepane **207a** (8:1 r.r.) with complete selectivity for the unsaturated compound. Thus, the regiochemical outcome of the (6+1) carbonylative cyclisation of substituted cyclopropane-based substrates is the *opposite* to what was expected based on previous studies. Mechanistic studies directed at understanding this phenomenon are presented in Section 2.1.4.2. McCreanor also synthesised and tested several other classes of substituted cyclopropane-based substrate in the (6+1) carbonylative cyclisation, and the results are presented in the proceeding sections.



Scheme 41: Regioselectivity of the (6+1) carbonylative cyclisation of *trans*- and *cis*-1,2-disubstituted cyclopropylureas.

1.4.3 Summary of McCreanor's investigations into the (6+1) carbonylative cyclisation

McCreanor's discovery of the (6+1) carbonylative cyclisation of cyclopropylureas *via* intramolecular nucleophilic addition to rhodacyclopentanones serves as a realisation of the general strategy outlined in Scheme 37. The optimised conditions tolerated simple primary alkyl substitution at the R^1 and R^2 positions but proved unsatisfactory in more challenging cases. 1,2-Disubstituted cyclopropanes were briefly investigated, which revealed a reversal in regioselectivity when compared to previous work carried out in Bristol. The switch in C4-C5 oxidation level selectivity observed in the reaction of *N*,*N*'-disubstituted cyclopropylurea **202a** (Table 2) raised the possibility of developing an oxidation level divergent synthesis of diazepanes.

1.5 Project aims

In the previous section, Shaw and McCreanor's development of a directing group strategy for the formation of rhodacyclopentanones and application to the synthesis of sp^3-rich heterobicyclic molecules at Bristol was described. McCreanor then made the discovery that rhodacyclopentanones could be trapped by nucleophiles, which resulted in the identification of the (6+1) carbonylative cyclisation of cyclopropylureas to form diazepanes. Nucleophilic addition to rhodacyclopentanones is an under-explored mode of reactivity, which holds great promise for the synthesis of valuable medium-sized rings.

The research described in this thesis is split into two Chapters. Chapter 2 details a project investigating nucleophilic addition to rhodacyclopentanones. The initial goal of this project was to develop improved reaction conditions for the (6+1) carbonylative cyclisation of cyclopropylureas and reinvestigate the scope of the transformation. Mechanistic studies were then to be carried out in order to understand the factors affecting C4-C5 oxidation level selectivity in the product diazepanes and the unexpected regioselectivity of Rh(I)-addition to substituted cyclopropanes. A second aim of this project was to test the generality of the intramolecular nucleophilic addition to rhodacyclopentanones in the hope that this strategy could be expanded to allow access to further heterocyclic structures.

The aim of Chapter 3 was to apply a rhodacyclopentanone-based methodology, developed at Bristol, to the total synthesis of a natural product. Here, Shaw's (7+1) carbonylative cyclisation of cyclopropylacrylamides was to be investigated as an asymmetric entry to the azocane ring system of the pyrrolizidine alkaloid, (*R*)-otonecine. A secondary aim of this project was to develop a short synthesis of the dicarboxylic necic acids, which, together with (*R*)-otonecine, form the other otonecine-type pyrrolizidine alkaloids. The successful synthesis of (*R*)-otonecine would constitute the first asymmetric total synthesis of this natural product, whereas none of the other otonecine-type PAs have been synthesised before.

Chapter 2 – Intramolecular nucleophilic addition to rhodacyclopentanones

Section 1.4.2 outlined McCreanor's discovery of the (6+1) carbonylative cyclisation of cyclopropylureas to form diazepanes by intramolecular nucleophilic addition to rhodacyclopentanones. The reaction conditions developed by McCreanor allowed the efficient cyclisation of simple substrates, but the scope of the cyclisation was narrow. Investigations described in this thesis began with the development of optimised conditions for the (6+1) carbonylative cyclisation.

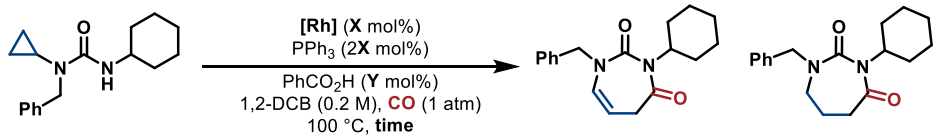
2.1 Further development of the (6+1) carbonylative cyclisation of cyclopropylureas

Aspects of this chapter have been adapted from a communication.

(McCreanor, N. G.[†]; Stanton, S.[†]; Bower, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 11465. [†]N. G. McCreanor and S. Stanton contributed equally)

2.1.1 Optimisation of the (6+1) carbonylative cyclisation of cyclopropylureas

The conditions developed by McCreanor allowed the (6+1) carbonylative cyclisation of parent trisubstituted cyclopropylurea **195a** in 96% yield and with high selectivity (15:1, **196a**:**197a**) over the saturated diazepane (Table 1). Cyclohexylurea **195g** was chosen as a substrate for further optimisation because it cyclised under McCreanor's conditions to form diazepane **196g** in only 39% yield with 35% of the starting material remaining (Entry 1, Table 3). This was presumably due to the large cyclohexyl R^2-substituent. Initially, several solvents (benzonitrile, anisole, PhMe, 1,4-dioxane) and triarylphosphine ligands were tested, but these did not improve the yield of diazepane **196g**. The Rh(I)-counterion was found to influence the reaction as illustrated by the improved yield of 44% of diazepane **196g** when 3.5 mol% of [Rh(cod)$_2$]BARF was employed (Entry 2). Further improvements were



Entry	[Rh]	X	Y	time	Yield[a] (196g:197g)	195g
1	[Rh(cod)$_2$]OTf	2.5	10	24 h	39% (19:1)	45%
2	[Rh(cod)$_2$]BARF	3.5	10	24 h	44% (17:1)	25%
3	[Rh(cod)$_2$]BARF	7.5	10	24 h	53% (20:1)	27%
4	[Rh(cod)$_2$]BARF	7.5	10	48 h	68% (18:1)	11%
5	**[Rh(cod)$_2$]BARF**	**7.5**	**15**	**72 h**	**69%[b] (23:1)**	**7%**

[a]*In-situ* NMR yield measured against an internal standard; [b]Isolated yield.

Table 3: Selected results from the optimisation of the (6+1) carbonylative cyclisation of cyclopropylurea **195g**.

obtained by increasing the catalyst loading (53% yield at 7.5 mol%, Entry 3) and the duration of the reaction (68% yield over 48 h, Entry 4). An acceptable isolated yield of 69% of diazepane **196g** was achieved by employing 7.5 mol% of $[Rh(cod)_2]$BARF and 15 mol% benzoic acid over 72 h (Entry 5). In all these studies, the unsaturated diazepane **196g** was formed with high selectivity (>15:1 **196g**: **197g**) over the saturated diazepane **196g**.

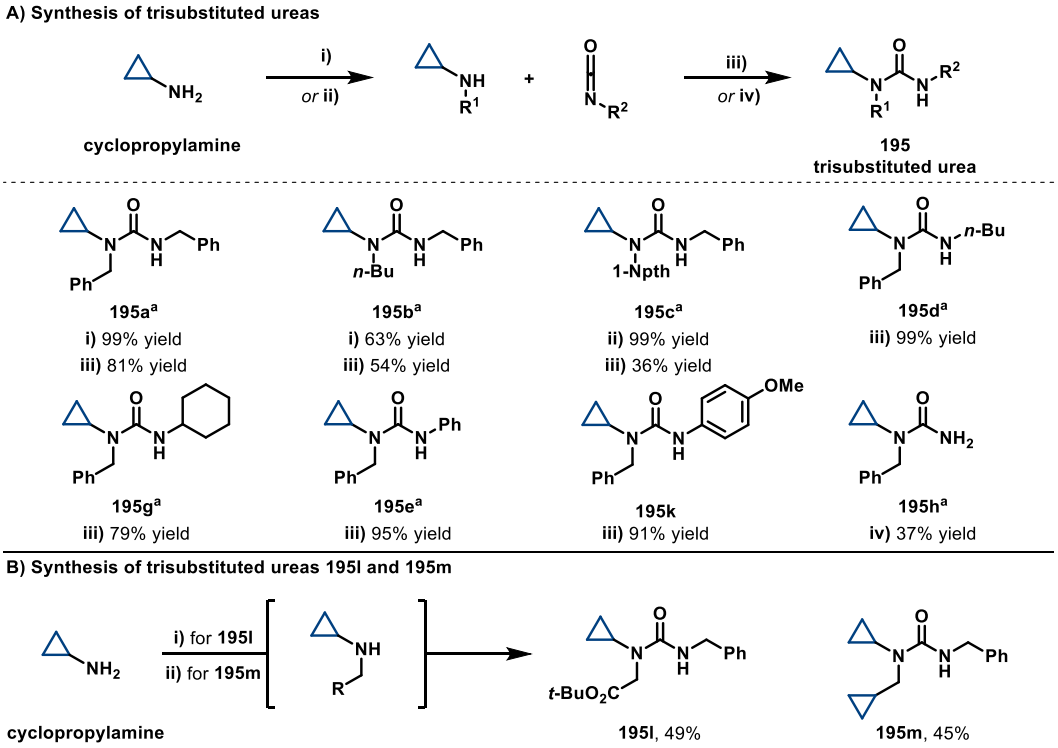
2.1.2 Scope of the (6+1) carbonylative cyclisation of cyclopropylureas

Having optimised the conditions for the (6+1) carbonylative cyclisation of "challenging" cyclohexylurea **195g**, the scope of the cyclisation was reinvestigated. In addition to trisubstituted cyclopropylureas, a range of *N*,*N*'-disubstituted cyclopropylureas were synthesised because it was observed that cyclisation of benzyl cyclopropylurea **202a** formed the C4-C5 *saturated* diazepane **204a** selectively (see Table 2).

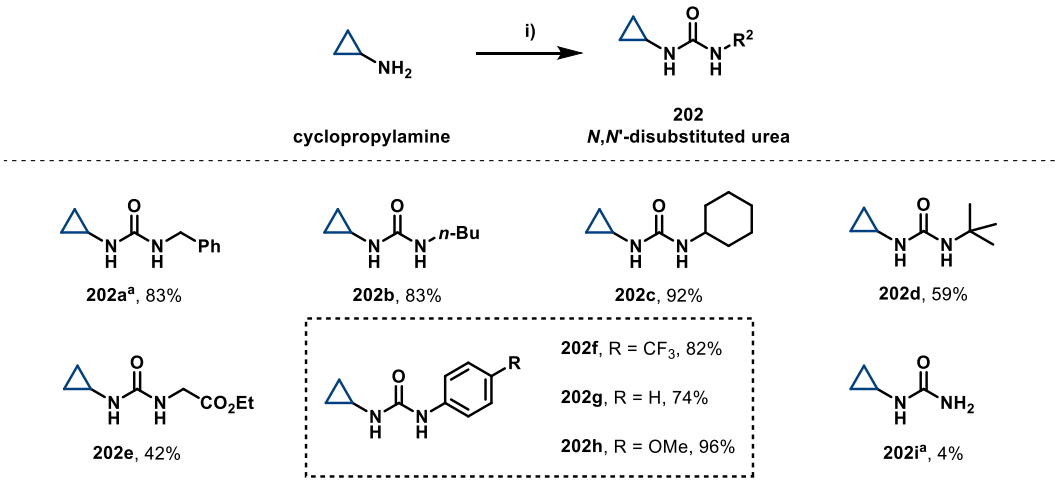
2.1.2.1 Synthesis of cyclopropylureas

McCreanor employed a two step sequence to synthesise several trisubstituted cyclopropylureas with various substituents at the R^1 and R^2 positions (Scheme 42A). The sequence began with the preparation of secondary amines by reductive amination of cyclopropylamine and the corresponding aldehyde, or by Buchwald-Hartwig cross-coupling in the case of naphthyl cyclopropylurea **195b**. The secondary amines were then coupled with either an isocyanate to form trisubstituted cyclopropylureas, or with *in-situ* generated isocyanic acid as in the case of *N*,*N*-disubstituted cyclopropylurea **195h**. Two additional trisubstituted cyclopropylureas **195l** and **195m** were synthesised by a streamlined procedure, which avoided the need to isolate the intermediate secondary amines (Scheme 42B). Aminoester derivative **195l** was synthesised in 49% yield by a one-pot procedure involving alkylation of cyclopropylamine with *t*-butyl bromoacetate followed by urea formation with benzyl isocyanate. Similarly, bis-cyclopropylurea **195m** was formed in 45% yield by alkylation of cyclopropylamine with (bromomethyl)cyclopropane and subsequent urea formation.

N,*N*-Disubstituted cyclopropylureas **202a-h** were prepared by reaction of cyclopropylamine with the corresponding isocyanate in generally excellent yield (42–96% yield) and in less than one hour from commercially available reagents (Scheme 43). Monosubstituted cyclopropylurea **202i** was prepared in 4% yield by reaction of cyclopropylamine with *in-situ* generated isocyanic acid.



Scheme 42: A) *Reagents and conditions*: i) corresponding aldehyde, $NaHCO_3$, MeOH, reflux, 16 h *then* $NaBH_4$, 0 °C to r.t., 16 h; ii) 2-Bromonaphthalene, $Pd_2(dba)_3$, BINAP, NaO*t*-Bu, PhMe, 80 °C, 16 h; iii) corresponding isocyanate, NEt_3, CH_2Cl_2, 0 °C to r.t., 1 h; iv) KOCN, aq. 5 M HCl, r.t., 36 h. B) *Reagents and conditions*: i) *t*-butyl bromoacetate, NEt_3, CH_2Cl_2, r.t., 7 h *then* benzyl isocyanate, r.t., 17 h, 49%; ii) (bromomethyl)cyclopropane, DMSO, r.t., 20 h *then* benzyl isocyanate, CH_2Cl_2, 0 °C to r.t., 16 h, 45%. [a]Synthesised by McCreanor.



Scheme 43: Synthesis of *N,N*'-disubstituted cyclopropylureas. *Reagents and conditions*: i) corresponding isocyanate, NEt_3, CH_2Cl_2, 0 °C to r.t., 1 h; *Compound **202i*** KOCN, aq. 5 M HCl. [a]Synthesised by McCreanor

2.1.2.2 (6+1) carbonylative cyclisation of trisubstituted cyclopropylureas

The newly optimised conditions for the (6+1) carbonylative cyclisation were used to reinvestigate the scope of the (6+1) carbonylative cyclisation (Table 4). The majority of trisubstituted

cyclopropylureas cyclised with high efficiency to afford diazepanes in greater than 60% yield and with essentially complete selectivity for the unsaturated product (typically >15:1, **196**:**197**). Alkyl and aryl R^1-substituents were well tolerated as shown by the formation of diazepanes **196a-c,l,m** in excellent yields (60–87% yield). It is noteworthy that the potentially labile *tert*-butyl ester of substrate **195l** remained intact to provide diazepane **196l** in 65% yield. Also, preferential Rh(I)-addition to the aminocyclopropane moiety of substrate **195m** to form diazepane **196m** (87% yield) in the presence of a second cyclopropane unit illustrates the exquisite C-C bond selectivity afforded by the directing group. Likewise, primary and secondary alkyl R^2-substituents were well tolerated as indicated by the formation of diazepanes **196d** and **196g** in 85% and 69% yield, respectively. Finally, *N*,*N*-disubstituted cyclopropylurea **195h** cyclised efficiently to form diazepane **196h** in 54% yield and with 8:1 selectivity over **197h**. It was discovered that trisubstituted cyclopropylureas containing aryl substituents at R^2 are a limitation of the methodology. For example, phenyl cyclopropylurea **195e** formed diazepane **196e** in only 28% yield. Similarly, electron-rich aryl cyclopropylurea **195k** cyclised to form diazepane **196k** in a similarly poor 28% yield, which suggests that the poor reactivity is not due to *N*-aryl nucleophiles being less nucleophilic.

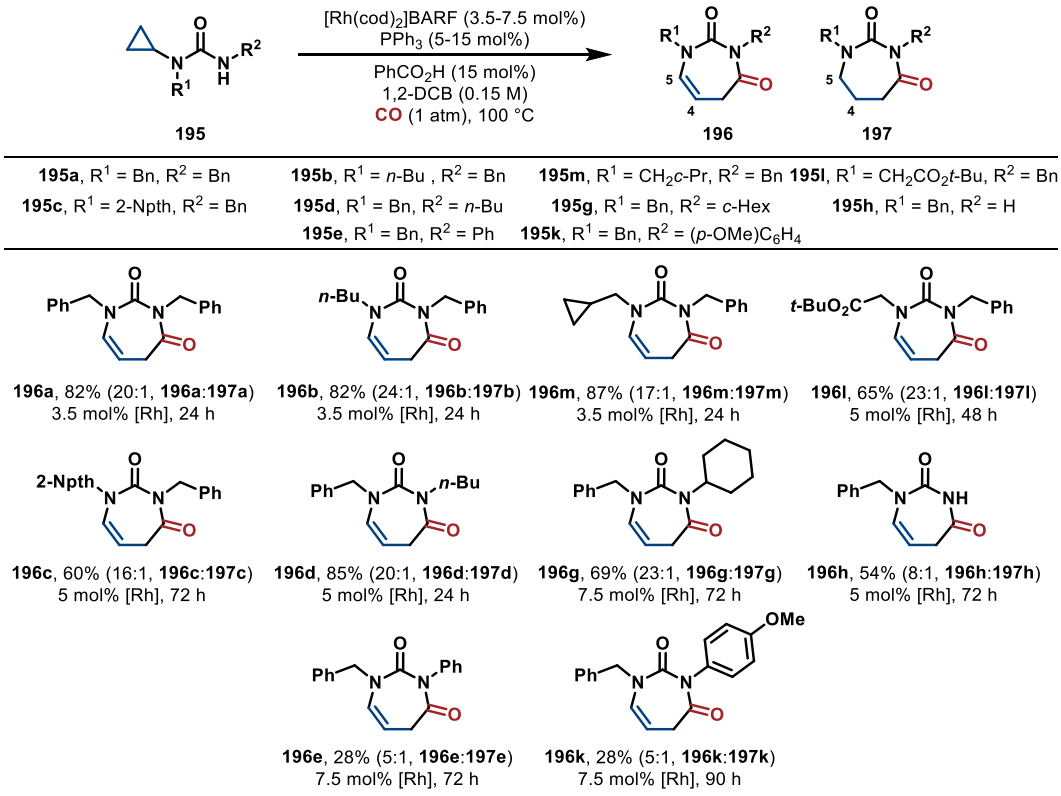


Table 4: Scope of the (6+1) carbonylative cyclisation of trisubstituted cyclopropylureas.

2.1.2.3 (6+1) carbonylative cyclisation of *N*,*N*'-disubstituted cyclopropylureas

The scope of the (6+1) carbonylative cyclisation with respect to *N*,*N*'-disubstituted cyclopropylureas was also investigated, and the results are shown in Table 5. Importantly, all the *N*,*N*'-

disubstituted cyclopropylureas favoured the formation of the saturated diazepane over the unsaturated variant. Thus, the C4-C5 oxidation level can be controlled by the choice of R^1-substituent: when R^1 = alkyl or aryl the unsaturated diazepane forms preferentially, but when R^1 = H the saturated diazepane forms preferentially. In general, the magnitude of the oxidation level selectivity of *N*,*N*'-disubstituted cyclopropylureas (>1:12, **203**:**204**) was less than for trisubstituted cyclopropylureas (typically >15:1, **196**:**197**). Mechanistic investigations into the factors governing oxidation level selectivity are presented in Section 2.1.4.1.

N,*N*'-Disubstituted cyclopropylureas bearing alkyl R^2-substituents were well tolerated in the cyclisation (see **204a-e**) including sterically demanding variants such as *tert*-butylurea **202d** (53% yield, 1:4 **203d**:**204d**). The successful cyclisation of *tert*-butylurea **202d** is significant as it suggests that Rh(I)-addition to the cyclopropyl C-C bond is *O*-directed and not *N*-directed. Oxidation level selectivity was insensitive to the size of the R^2-group (compare **204b**, **204c**, **204d**), but was affected by the electronics of the nucleophile. For example, less nucleophilic aminoester **202e** formed saturated product **204e** in a 1:1 ratio with its unsaturated analogue **203e**.

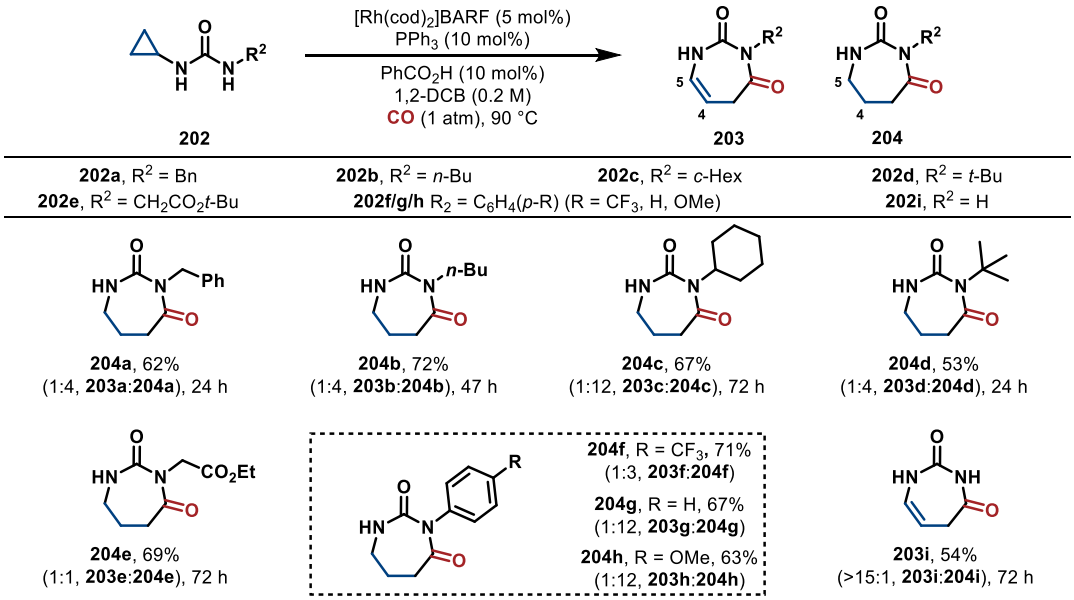


Table 5: Scope of the (6+1) carbonylative cyclisation of *N*,*N*'-disubstituted cyclopropylureas.

Interestingly, *N*-aryl nucleophiles performed well in the (6+1) carbonylative cyclisation of *N*,*N*'-disubstituted cyclopropylureas, which contrasts trisubstituted cyclopropylureas where *N*-aryl nucleophiles are a limitation (see **196e/k**, Table 4). Phenylcyclopropylurea **202g** reacted to form cyclisation product **204g** in 67% yield and with good selectivity for the saturated product (1:12, **203g**:**204g**). The nucleophilicity of the *N*-aryl nucleophile was varied by incorporation of different *para*-substituents (see **202f** (R = CF_3) and **202h** (R = OMe)) on the aryl ring. Both aryl ureas **202f** and **202h** cyclised in high yield (71% and 63%, respectively), but electron-deficient aryl urea **202f** was less selective for the saturated diazepane **204f** (1:3 **203f**:**204f** vs. 1:12 **203h**:**204h**). Finally, monosubstituted

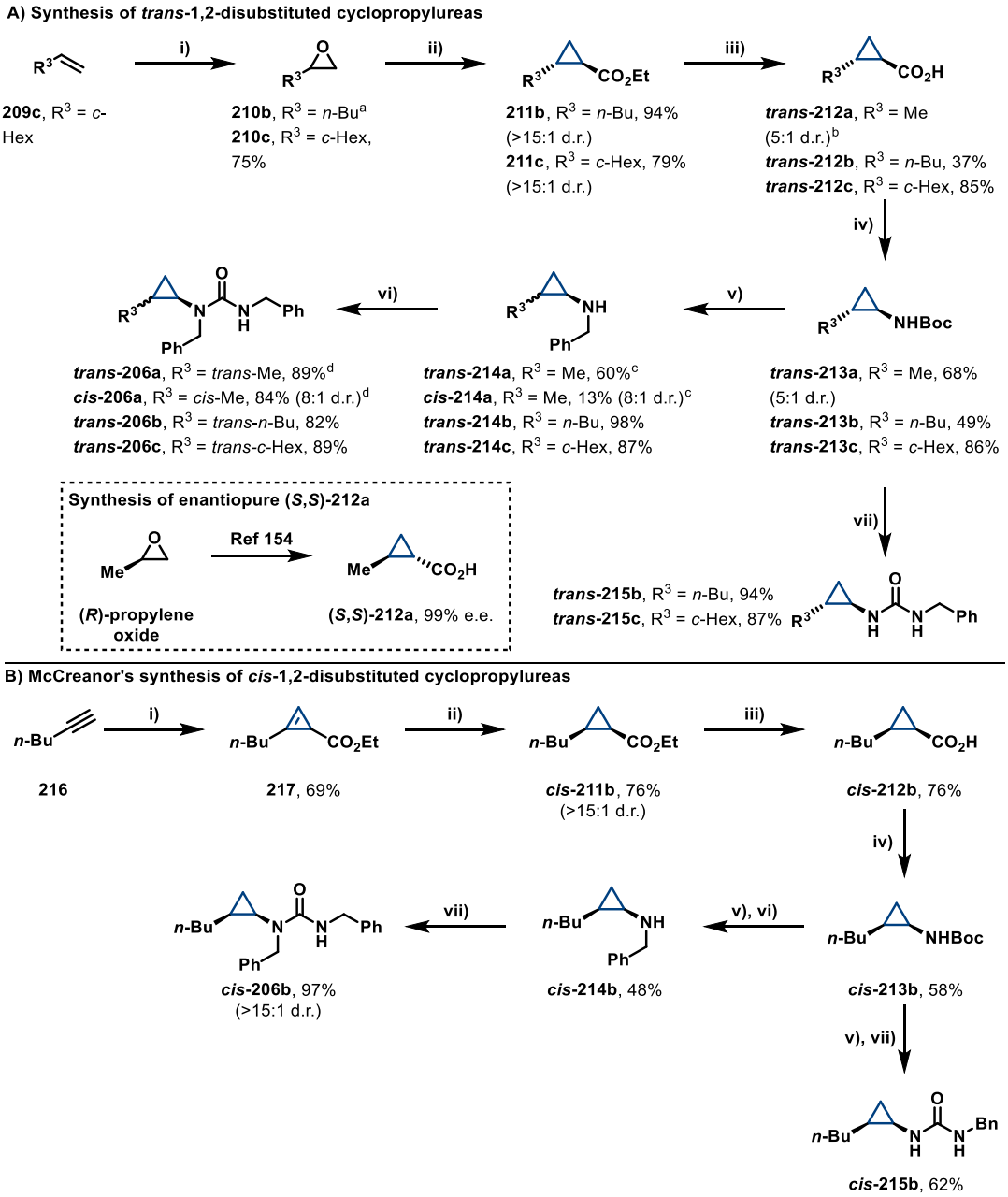
cyclopropylurea **202i** cyclised to form the unsaturated diazepane **203i** in 54% isolated yield. The reported selectivity of the cyclisation of cyclopropylurea **202i** reflects the fact that it was purified by filtration due to the low solubility of this compound.

2.1.3 Scope of the (6+1) carbonylative cyclisation of substituted cyclopropanes

The optimised conditions for the (6+1) carbonylative cyclisation allowed the cyclisation of a diverse selection of trisubstituted and *N*,*N*'-disubstituted cyclopropylureas in generally high yields and with control over the oxidation level of the C4-C5 position. Next, the scope of the optimised conditions with respect to substrates composed of 1,2-disubstituted cyclopropanes and fused cyclopropanes was reinvestigated. In particular, further information was required in order to explain the unexpected regioselectivity of Rh(I)-addition to *trans*- and *cis*-1,2-disubstituted cyclopropanes (see Section 1.4.2.2). Several representative 1,2-disubstituted cyclopropane-based substrates were prepared with simple alkyl R^3-substituents (R^3 = Me, *n*-Bu and *c*-Hex) of varying size. Additionally, fused cyclopropanes were investigated in the (6+1) carbonylative cyclisation.

2.1.3.1 Synthesis of cyclopropylureas containing 1,2-disubstituted cyclopropanes

In addition to the substrates containing 1,2-disubstituted cyclopropanes synthesised by McCreanor (indicated in Scheme 44), several others examples were prepared following a previously reported route (Scheme 44A).[102] Initially, cyclohexylepoxide **210c** was obtained by epoxidation of vinylcyclohexane **209c** in 75% yield. Epoxides **210b** (commercially available) and **210c** underwent *trans*-selective Wadsworth-Emmons cyclopropanation with triethylphosphonoacetate (TEPA) to furnish cyclopropyl esters **211b** and **211c** in 94% and 79% yield, respectively.[153] Hydrolysis then provided carboxylic acids **212b** and **212c**. Carboxylic acids **212a-c** (**212a** was commercially available in a 5:1 d.r.) underwent Curtius rearrangement with diphenylphosphoryl azide (DPPA) in *t*-BuOH to provide Boc-protected amines ***trans*-213a-c**. Boc-deprotection using trifluoroacetic acid, and reductive amination with benzaldehyde provided benzyl amines ***trans*-214a-c**. At this point, diastereomers ***trans*-214a** and ***cis*-214b** were separated by column chromatography, which provided access to both diastereomers of the (7+1) substrate. Benzyl amines **214a-c** were treated with benzyl isocyanate to form the trisubstituted *trans*-cyclopropylureas ***trans*-206a-c** and ***cis*-206a** in 82–89% yield. Additionally, *N*,*N*'-disubstituted *trans*-cyclopropylureas ***trans*-215b** and ***trans*-215c** were formed in excellent yields from Boc-protected cyclopropylamines ***trans*-213b** and ***trans*-213c** by Boc-deprotection and urea formation. Enantioenriched *trans*-methyl cyclopropylcarboxylic acid **(*S*,*S*)-208a** was prepared from commercially available (*R*)-propylene oxide by a reported procedure[154] and was advanced to enantiopure cyclopropylurea **(*S*,*S*)-206a** (99% e.e., not shown) by the same route.



Scheme 44: A) Compounds ***trans*-206a** and ***cis*-206a** were prepared by McCreanor. *Reagents and conditions*: i) *m*-CPBA, CH_2Cl_2, 0 °C to r.t., 18 h, 75%; ii) triethylphosphonoacetate, *n*-BuLi, 1,2-DME, 130 °C, 18 h; iii) 4 M aq. NaOH, MeOH, r.t., 18 h; iv) DPPA, NEt_3, *t*-BuOH, 80 °C, 17 h; v) TFA, CH_2Cl_2, r.t., 30 min *then* benzaldehyde, $NaHCO_3$, MeOH, reflux, 18 h *then* $NaBH_4$, 0 °C to r.t., 18 h; vi) benzyl isocyanate, CH_2Cl_2, r.t., 1 h; vii) TFA, CH_2Cl_2, 0 °C to r.t., 30 min *then* benzyl isocyanate, CH_2Cl_2, r.t., 1 h. [a]Commercially available. [b] Commercially available in 5:1 (*trans*:*cis*) d.r.. [c]*Trans*- and *cis*-diastereomers were separated by chromatography. [d]Synthesised by McCreanor. B) *Reagents and conditions*: i) ethyl diazoacetate, $Rh_2(OAc)_4$, CH_2Cl_2, r.t., 16 h; ii) Lindlar's catalyst, H_2 (1 atm), EtOAc, r.t., 3 h; iii) NaOH, MeOH, r.t., 16 h; iv) DPPA, NEt_3, *t*-BuOH, reflux, 48 h; v) TFA, CH_2Cl_2, r.t., 16 h; vi) benzaldehyde, $NaHCO_3$, MeOH, reflux, 16 h *then* $NaBH_4$, 0 °C to r.t., 16 h; vii) benzyl isocyanate, NEt_3, CH_2Cl_2, 0 °C to r.t., 1 h.

The synthesis of *cis*-cyclopropylurea ***cis*-206b** was carried out by McCreanor (Scheme 44B). 1-Hexyne underwent $Rh_2(OAc)_4$-catalysed cyclopropenation with ethyl diazoacetate to form cyclopropene **217** in 69% yield. The *cis*-stereochemistry of the cyclopropane substituents was installed by heterogeneous hydrogenation of cyclopropene **217** using Lindlar's catalyst to provide *cis*-cyclopropane ***cis*-211b** in 76% yield as a single diastereomer. The remaining steps to form *cis*-substituted cyclopropylureas ***cis*-206b** and ***cis*-215b** were analogous to that described for *trans*-cyclopropylureas.

2.1.3.2 (6+1) carbonylative cyclisation of *trans*-1,2-disubstituted cyclopropylureas

The substituted cyclopropylureas were subjected to the optimised (6+1) carbonylative cyclisation conditions. Previously, McCreanor observed that *trans*-cyclopropylurea ***trans*-206a** reacted *via* Rh(I)-addition to the more hindered cyclopropyl C-C bond "*a*" as opposed to bond "*b*" to provide C3-substituted diazepanes, which contrasted previous studies at Bristol (see Section 1.3.3). Under the optimised (6+1) carbonylative cyclisation conditions, trisubstituted cyclopropylureas containing *trans*-1,2-disubstituted cyclopropanes ***trans*-206a** and ***trans*-206b** also reacted *via* more hindered bond "*a*" to form C3-substituted diazepanes **208a** and **208b** in 70% and 59% yield, respectively (Table 1). By increasing the size of the cyclopropane R^3-substituent the yield decreased as shown by *trans*-cyclopropylurea ***trans*-206c**, which formed cyclohexyl-substituted diazepane **208c** in 29% yield after 73 h. Importantly, cyclisation of enantiopure *trans*-cyclopropylurea **(*S*,*S*)-206a** proceeded to form enantiopure diazepane **(*S*)-208a** with complete retention of the R^3-substituted stereocentre (99% e.e.). This result confirms that the rhodacyclopentanone is configurationally stable under the reaction conditions. In each of these studies, the unsaturated products were formed as the sole product; the saturated diazepanes were not observed.

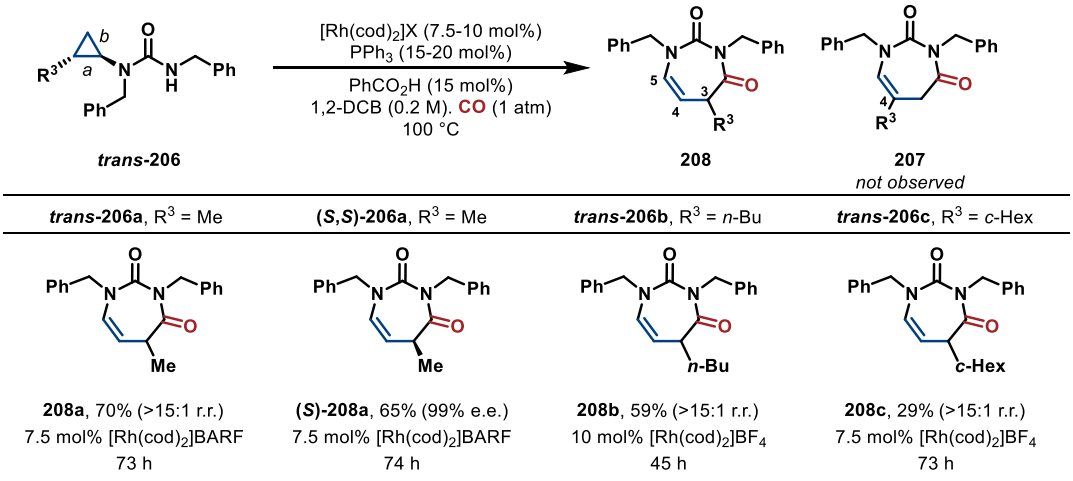


Table 6: Scope of the (6+1) carbonylative cyclisation of trisubstituted cyclopropylureas containing *trans*-1,2-disubstituted cyclopropanes.

N,*N*'-Disubstituted cyclopropylureas containing *trans*-1,2-disubstituted cyclopropanes were poor substrates for (6+1) carbonylative cyclisation because they formed complex mixtures of diazepanes (Table 7). For example, cyclisation of cyclopropylurea ***trans*-215b** proceeded with both low oxidation level selectivity (1:3, unsat:sat) and low regioselectivity (~1:1 r.r.) resulting in the formation of a complex mixture of four diazepanes (62% combined yield, ~1:4:1:2 **218b**:**219b**:**220b**:**221b**). The low regioselectivity observed for *N*,*N*'-disubstituted cyclopropylureas is in contrast to the trisubstituted cyclopropylureas presented in Table 6. Cyclohexyl-substituted cyclopropane ***trans*-215c** provided a similar product distribution and yield (57% combined yield, ~1:7:1:2, **218c**:**219c**:**220c**:**221c**).

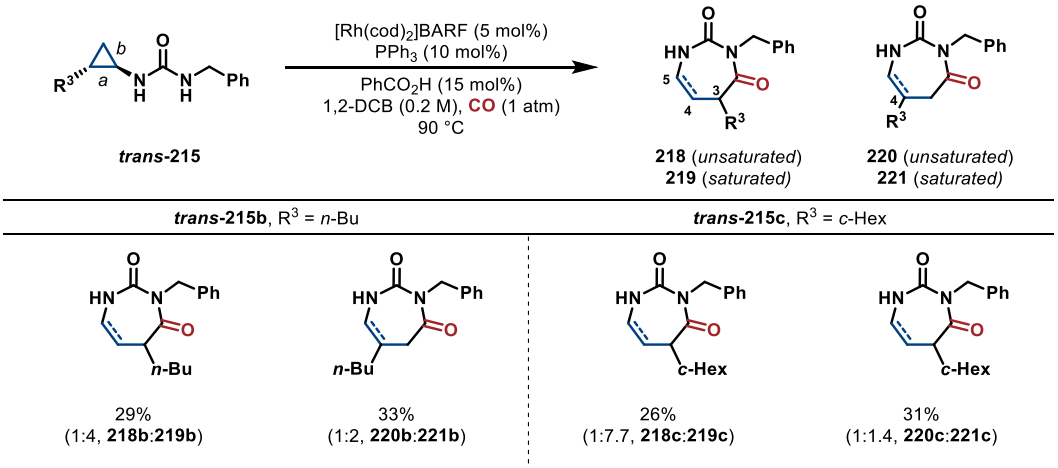


Table 7: Scope of the (6+1) carbonylative cyclisation of disubstituted cyclopropylureas containing *trans*-1,2-disubstituted cyclopropanes.

2.1.3.3 (6+1) carbonylative cyclisation of *cis*-1,2-disubstituted cyclopropylureas

Previously, McCreanor observed that *cis*-cyclopropylurea ***cis*-206a** reacted *via* Rh(I)-addition to the less hindered cyclopropyl C-C bond "*b*" as opposed to bond "*a*" to provide predominantly C4-substituted diazepanes, which contrasted previous studies at Bristol (see Section 1.3.3). Under the optimised cyclisation conditions, *cis*-cyclopropylureas ***cis*-206a,b** and ***cis*-215b** reacted in accordance with McCreanor's findings. For example, trisubstituted cyclopropylureas ***cis*-206a** and ***cis*-206b** cyclised to form the C4-substituted diazepanes **207a** and **207b** with moderate regioselectivity (5:1 r.r. for **207a** and 6:1 r.r. for **207b**), but with complete selectivity for the unsaturated diazepane (Table 8). *N*,*N*'-Disubstituted cyclopropylurea ***cis*-215b** also cyclised *via* Rh(I)-addition to cyclopropyl C-C bond "*b*", but with the characteristic reversal in oxidation level selectivity observed for *N*,*N*'-disubstituted cyclopropylureas (see Section 2.1.2.3), to form saturated diazepane **221b** (58%, 5:1 r.r.).

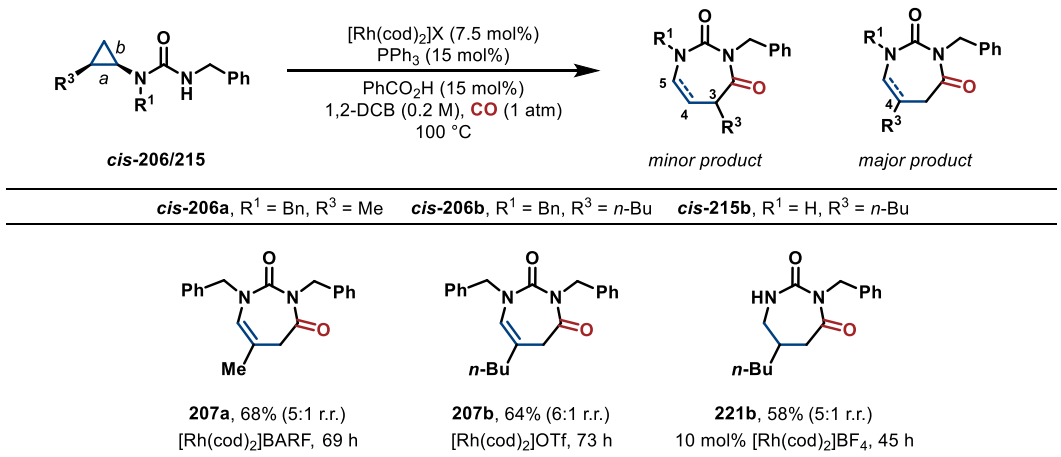
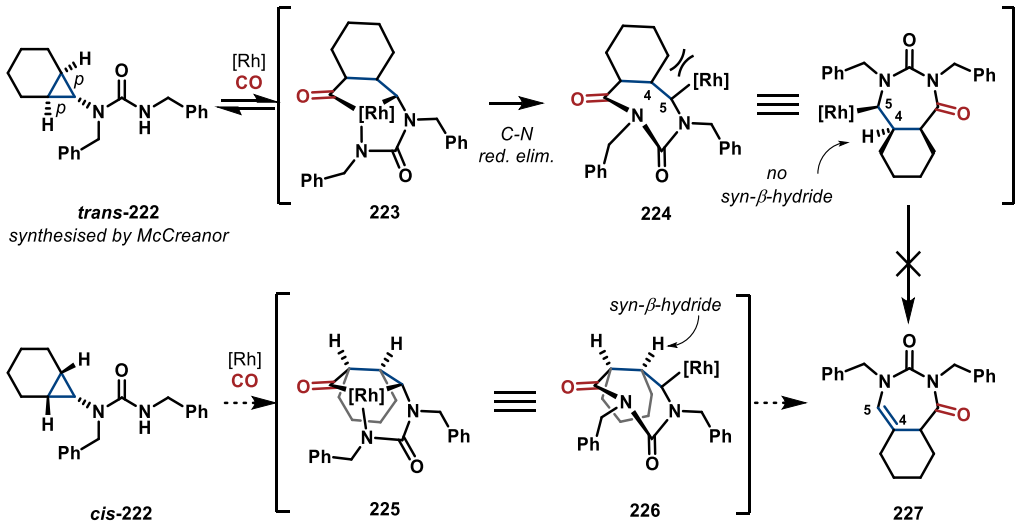


Table 8: Scope of the (6+1) carbonylative cyclisation of cyclopropylureas containing *cis*-1,2-disubstituted cyclopropanes.

2.1.3.4 Fused cyclopropylureas

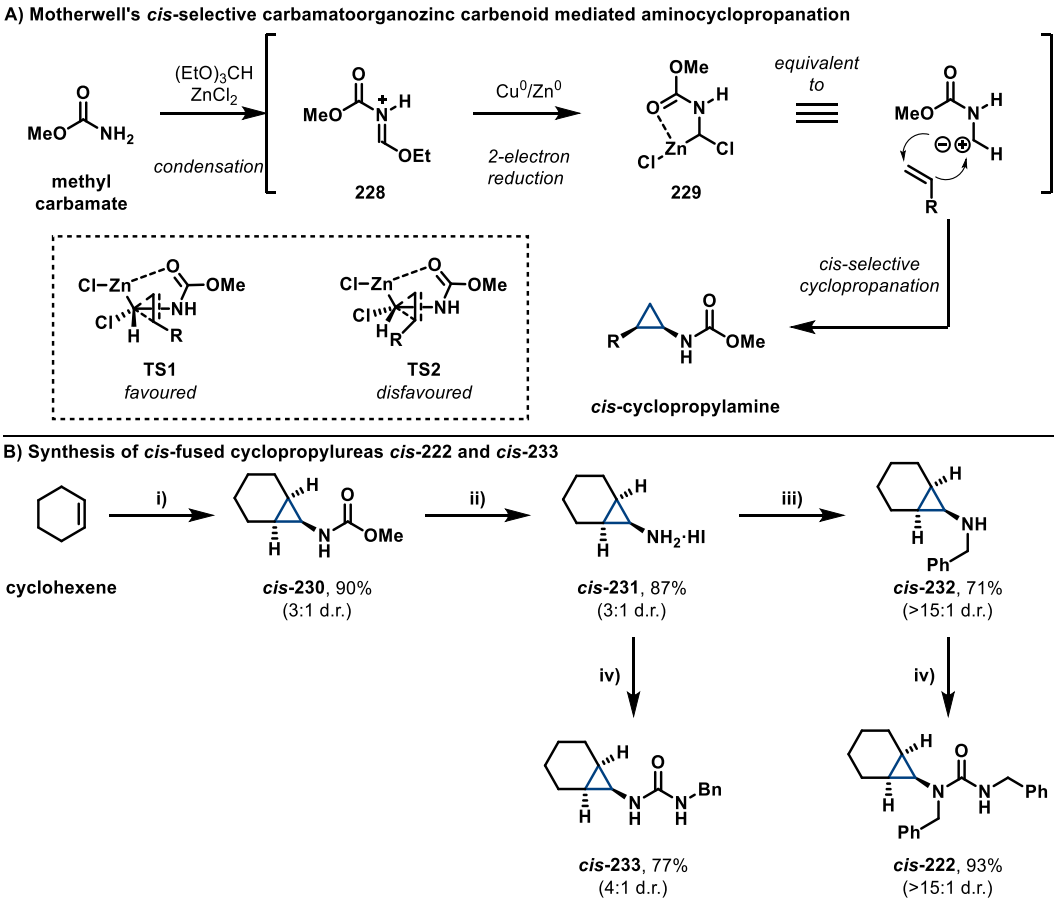
Cyclopropylureas containing fused cyclopropanes are valuable substrates for the (6+1) carbonylative cyclisation because they provide access to bicyclic diazepanes. Also note that the proximal C-C bonds of fused cyclopropanes (see bonds "*p*", Scheme 45) are chemically identical, which eliminates the issue of regioselectivity in the Rh(I)-addition step. Previously, McCreanor discovered that cyclopropylurea ***trans*-222**, which contains a *trans*-fused cyclopropane, failed to undergo (6+1) carbonylative cyclisation (Scheme 45). It was proposed that the failure to cyclise was a result of a developing steric clash between the [Rh]-centre and fused-cyclohexane ring during C-N reductive elimination from rhodacyclopentanone **223**. Additionally, the [Rh]-centre of resulting diazepane **224** does not possess a *syn*-β-hydrogen for β-hydride elimination. It was proposed that the *cis*-fused diastereomer ***cis*-222**, would be a suitable substrate for cyclisation because C-N reductive elimination from the corresponding rhodacyclopentanone, **225**, would be accompanied by a minimal developing



Scheme 45: Mechanistic rationale for the failed cyclisation of *trans*-fused cyclopropylurea ***trans*-222**.

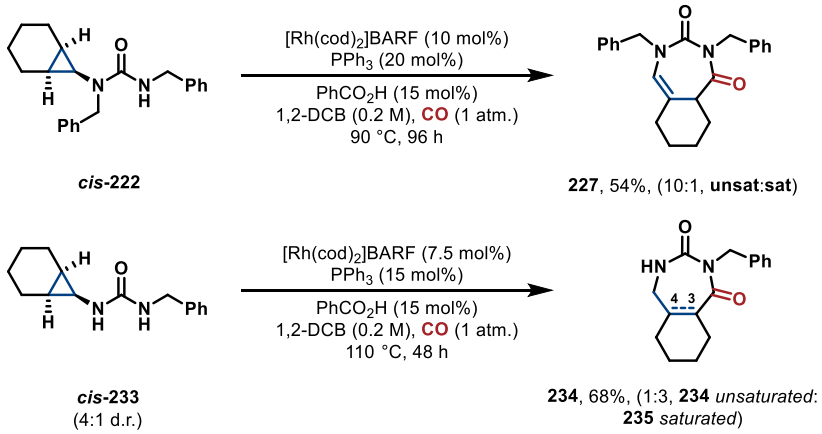
steric clash. Furthermore, the [Rh]-centre of intermediate **226** possesses a *syn*-β-hydrogen in order to form product **227**. To test this hypothesis, *cis*-fused cyclopropane ***cis*-222** was synthesised and subjected to the cyclisation conditions.

The synthesis of *cis*-fused cyclopropane ***cis*-222** was achieved using a *cis*-diastereoselective carbamatoorganozinc carbenoid-mediated aminocyclopropanation of alkenes, reported by Motherwell (Scheme 46A).[155] The proposed mechanism of Motherwell's reaction proceeds by Lewis acid-mediated condensation of methyl carbamate with triethyl orthoformate to form iminium species **228**. Iminium **228** is reduced by a zinc/copper amalgam to form zinc(II)-species **229**, which serves as a carbene equivalent in the cyclopropanation of alkenes. Motherwell suggests that the *cis*-diastereoselectivity arises as a result of preferential approach of the alkene to zinc(II)-species **229**, such that the R-substituent is directed away from the bulky zinc centre (i.e. **TS1** is favoured over **TS2**).



Scheme 46: B) *Reagents and conditions*: i) methyl carbamate, Cu powder, Zn powder, $ZnCl_2$, TMSCl, $(EtO)_3CH$, Et_2O, r.t., 18 h; ii) TMSI, CH_2Cl_2, reflux, 1 h *then* MeOH, reflux, 30 min; iii) benzaldehyde, $NaHCO_3$, MeOH, reflux, 16 h *then* $NaBH_4$, 0 °C to r.t., 12 h; iv) benzyl isocyanate, NEt_3, CH_2Cl_2, 0 °C to r.t., 1 h.

Under Motherwell's conditions, cyclohexene underwent aminocyclopropanation to form *cis*-fused aminocyclopropane ***cis*-230** in 90% yield and 3:1 d.r. (Scheme 46B). The carbamate of aminocyclopropane ***cis*-230** was removed in 87% yield using iodotrimethylsilane, and the resulting amine hydroiodide salt ***cis*-231** underwent efficient reductive amination with benzaldehyde to form benzyl amine ***cis*-232** in 71% yield. At this point the *trans*- and *cis*-diastereomers were partially separated by chromatography. Urea formation with benzyl isocyanate (93%) provided *cis*-fused substrate ***cis*-222** as a single diastereomer. Additionally, *N*,*N*'-disubstituted cyclopropylurea ***cis*-233** was prepared by urea formation directly from amine hydroiodide salt ***cis*-231** in 77% yield and 4:1 d.r. (inseparable mixture). Under the optimised (6+1) carbonylative cyclisation conditions, *cis*-fused substrate ***cis*-222** formed bicyclic diazepane **227** in 54% yield (Scheme 47) thereby confirming the hypothesis proposed in Scheme 45. Additionally, *N*,*N*'-disubstituted substrate ***cis*-233** (4:1 d.r.) cyclised to form a mixture of bicyclic diazepanes **234** (C3-C4 unsaturated) and **235** (C3-C4 saturated), where the alkene migrated into the presumably more stable tetrasubstituted position.



Scheme 47: (6+1) carbonylative cyclisation of *cis*-fused cyclopropylureas.

In conclusion, the optimised conditions for the (6+1) carbonylative cyclisation allow the efficient cyclisation of a diverse selection of trisubstituted and *N*,*N*'-disubstituted cyclopropylureas including multiple examples bearing substituted cyclopropanes. At this point, efforts were directed to gaining a better understanding of the mechanism of the (6+1) carbonylative cyclisation. In particular, an understanding of the factors which govern the oxidation level of the C4-C5 positions of the diazepanes and the regioselectivity of reactions involving 1,2-disubstituted cyclopropanes was desired.

2.1.4 Mechanistic Studies into the (6+1) carbonylative cyclisation

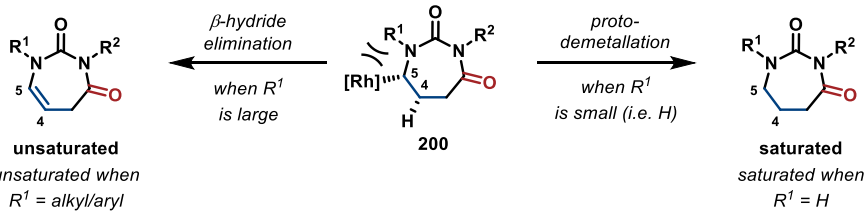
Mechanistic studies were conducted to gain a better understanding of the factors that govern the oxidation level selectivity of the C4-C5 position of diazepanes (Section 2.1.2.2 and 2.1.2.3) and the unexpected regioselectivity of C-C oxidation addition to 1,2-disubstituted cyclopropanes (Section

2.1.3). Information obtained in these studies is of general interest to the broader project because it might aid the control of selectivity in related processes.

2.1.4.1 C4-C5 oxidation level selectivity

Previously it had been observed that the oxidation level of the C4-C5 position of diazepanes could be controlled by the choice of R^1-substituent; specifically when R^1 = alkyl or aryl the unsaturated diazepane forms preferentially, but when R^1 = H the saturated diazepane forms preferentially. Efforts to override the substrate dependent selectivity by altering the cyclisation conditions failed, further highlighting the importance of the R^1-substituent (Section 1.4.2.1). Notably, varying the amount of benzoic acid additive did not influence the oxidation level selectivity, which indicates that protodemetallation from intermediate **200** (see Scheme 48) might not be promoted by the addition of more acid.

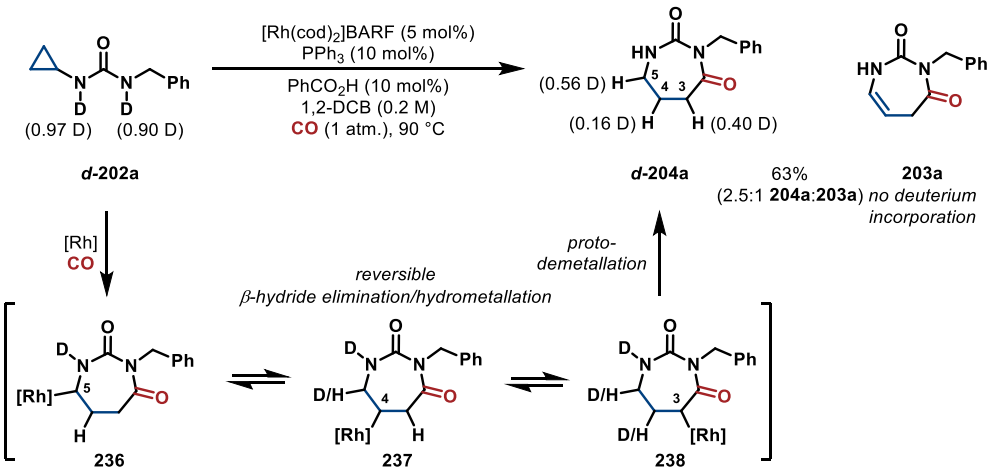
It was originally proposed that the importance of the R^1-substituent in determining the oxidation level of diazepanes was due to a steric interaction between the Rh(I)-moiety and R^1-substituent of intermediate **200** (Scheme 48). When R^1 is large (i.e. alkyl or aryl), the Rh(I)-moiety is pushed towards the C4-*syn*-β-hydrogen thereby promoting β-hydride elimination. In contrast, when R^1 is small (i.e. R^1 = H) the steric repulsion is minimised, increasing the lifetime of intermediate **200** and resulting in a higher degree of protodemetallation. This mechanistic proposal was investigated by performing a deuterium incorporation experiment with deuterated *N*,*N*'-disubstituted cyclopropylurea ***d*-202a** (Scheme 49). In this way, the site of protodemetallation would be indicated by the presence of deuterium in the product diazepane **204a**.



Scheme 48: Initial rationale for C4-C5 oxidation level selectivity afforded by the R^1-substituent.

Initially, deuterated *N*,*N*'-disubstituted cyclopropylureas ***d*-202a** (>95% deuterium incorporation at the indicated positions) was prepared by dissolving cyclopropylurea **202a** in d_4-methanol and concentrating *in vacuo* three times (Scheme 49). Upon cyclisation, cyclopropylurea ***d*-202a** provided diazepanes ***d*-204a** and **203a** in 65% yield (2.5:1 ***d*-204a**:**203a**). Analysis of the product mixture by ^{1}H and ^{2}D-NMR revealed that saturated diazepane ***d*-204a** had significant deuterium incorporation at positions C3 (0.40 D), C4 (0.16 D) and C5 (0.56 D). No deuterium was observed on unsaturated diazepane **203a**. Incomplete deuterium incorporation in saturated product ***d*-204a** is likely due to the presence of protic impurities, such as water, in the reaction solvent.

The result of the deuterium incorporation experiment on ***d*-202a** cannot be fully explained by the mechanism proposed in Scheme 48. Deuterium incorporation at C5 of saturated diazepane ***d*-204a** was expected, and presumably results from deuterodemetallation from intermediate **236** (Scheme 49). Deuterium incorporation at C4 and C3 was not expected, but might be explained by a *reversible* sequence of β-hydride elimination and hydrometallation steps from intermediate **236**, which would provide access to regioisomers **237** and **238**. Deuterodemetallation from intermediates **237** and **238** would explain the observed deuterium incorporation at C4 and C3 of saturated diazepane ***d*-204a**. At the time being it is not understood why no deuterium is incorporated into unsaturated diazepane **203a**.

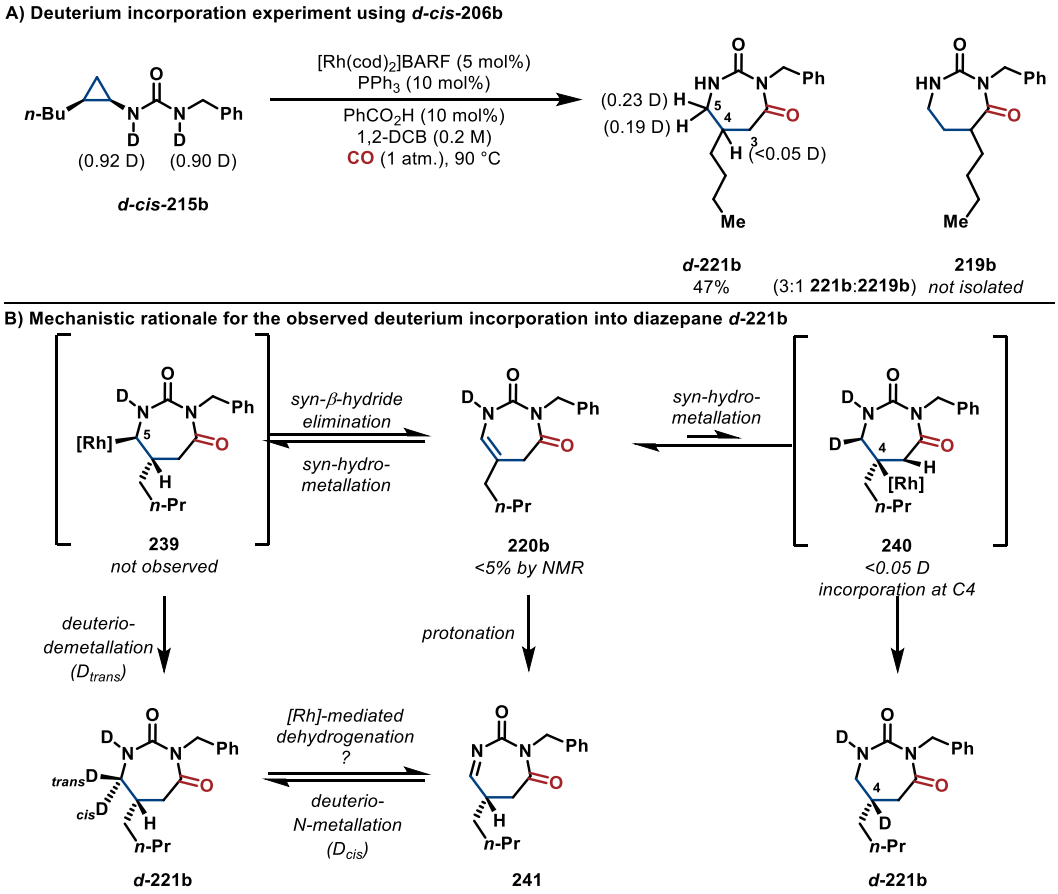


Scheme 49: Deuterium incorporation experiment using ***d*-202a** and proposed reversible β-hydride elimination.

To provide further evidence for the reversible β-hydride elimination step implicated in Scheme 49, a second deuterium incorporation experiment was performed on *cis*-1,2-disubstituted cyclopropylurea ***d-cis*-215b** (Scheme 50). It was postulated that the presence of a C4-*n*-butyl substituent would hinder the reversible β-hydride elimination step resulting in less deuterium being incorporated at C4 and C3 of diazepane ***d*-221b**. Deuterated substrate ***d-cis*-215b** was prepared in an identical manner to ***d*-202a**. Under the (6+1) carbonylative cyclisation conditions, C4-substituted diazepane ***d*-221b** was isolated in 47% yield, but the C3-regioisomer **219b** was not isolated. ^{1}H and ^{2}D-NMR analysis of C4-substituted diazepane ***d*-221b** showed deuterium incorporation at both diastereotopic C5-positions, D_{trans} (0.23 D) and D_{cis} (0.19 D), and a trace amount at C4 (<0.05 D). No deuterium incorporation was measured at C3, which reduces the possibility of a deprotonation/deuteration sequence being responsible for deuteration of the C3-position of ***d*-204a** in the experiment above (Scheme 49).

Once again, the result of the deuterium incorporation experiment on ***d-cis*-215b** cannot be fully explained by the mechanism proposed in Scheme 49. Deuterium incorporation at D_{trans} and C4 was expected, and is presumably a result of deuterodemetallation from intermediates **239** and **240**, respectively. The lower magnitude of deuterium incorporation at C4 (<0.05%) of ***d*-221b** was also predicted as a result of an unfavourable equilibrium between C5-metallated intermediate **239** and C4-

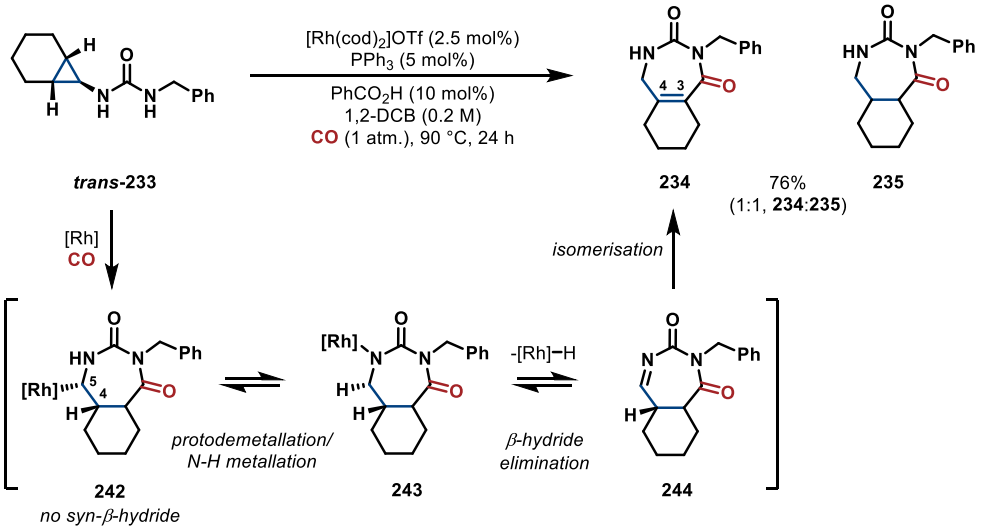
metallated intermediate **240**. However, deuteration of the C5-diastereotopic position, D_{cis}, is not explained by reversible β-hydride elimination because β-hydride elimination and hydrometallation are *syn*-specific processes. Therefore, deuteration of D_{cis} is proposed to proceed *via* intermediate imine **241** from which deuterometallation could occur from either diastereotopic face of the imine. Imine **241** could arise by two routes; tautomerisation of unsaturated diazepane **220b** under the acidic conditions of the (6+1) carbonylative cyclisation, or by metallation of the N-H bond of saturated diazepane ***d*-221b** followed by C5-β-hydride elimination. The second mechanistic proposal, involving N-H metallation and β-hydride elimination, is proposed because of an observation made by McCreanor regarding the successful cyclisation of *trans*-fused-cyclopropane ***trans*-233**.



Scheme 50

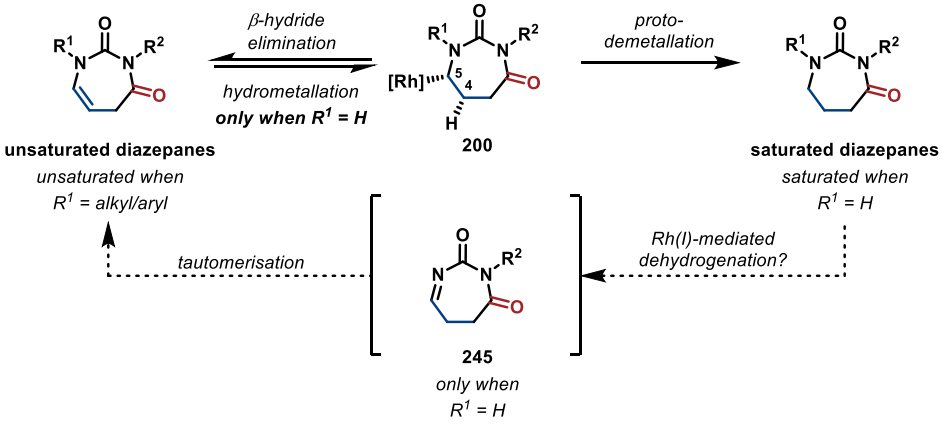
McCreanor found that *N*,*N*'-disubstituted cyclopropylurea ***trans*-233**, which is composed of a *trans*-fused cyclopropane, underwent successful cyclisation to form bicyclic diazepanes **234** and **235** in a 1:1 ratio and in 76% combined yield (Scheme 51). The formation of saturated **235** was expected (i.e. by protodemetallation from intermediate **242**), but it was not clear how unsaturated diazepane **234** was formed because β-hydride elimination from intermediate **242** cannot take place due to the absence of a *syn*-β-hydrogen to the [Rh]-centre. It was proposed that N-H metallation of saturated product **235** by a Rh(I)-species gives Rh(I)-amine complex **243** from which β-hydride elimination forms imine **244**.

Rh(I)-mediated dehydrogenation of secondary amines is a known process.[156-157] Tautomerisation of the unsaturation of imine **244**, to the presumably more stable tetrasubstituted position, provides diazepane **234**. Alternatively, β-hydride elimination from intermediate **242** would give direct access to imine **244**, however this was deemed unlikely because electron-withdrawing β-substituents are known to retard β-hydride elimination.[158] It would be informative to resubject pure saturated **235** to the cyclisation conditions to prove if this is indeed an intermediate in the formation of unsaturated **234**, but this experiment was not carried out.



Scheme 51: Mechanistic rationale for the (6+1) carbonylative cyclisation of *N*,*N*'-disubstituted *trans*-fused cyclopropylurea ***trans*-233**.

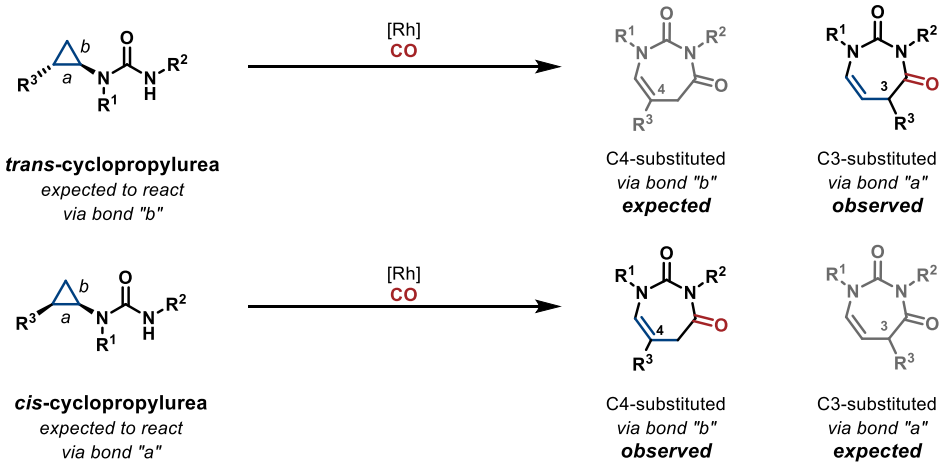
The deuterium incorporation studies detailed in this section demonstrate that reversible β-hydride elimination from intermediates **200** is operative when R^1 is small (i.e. R^1 = H), which, in turn, promotes the formation of saturated diazepanes (Scheme 52). However, preliminary evidence obtained from the reaction of *cis*-1,2-disubstituted cyclopropane ***cis*-206b** suggests that unsaturated diazepanes may also be formed by the Rh(I)-mediated dehydrogenation of saturated diazepanes. Further evidence to this effect may be gained by resubjecting saturated diazepanes to the reaction conditions.



Scheme 52: Current mechanistic understanding of the factors affecting C4-C5 oxidation level selectivity.

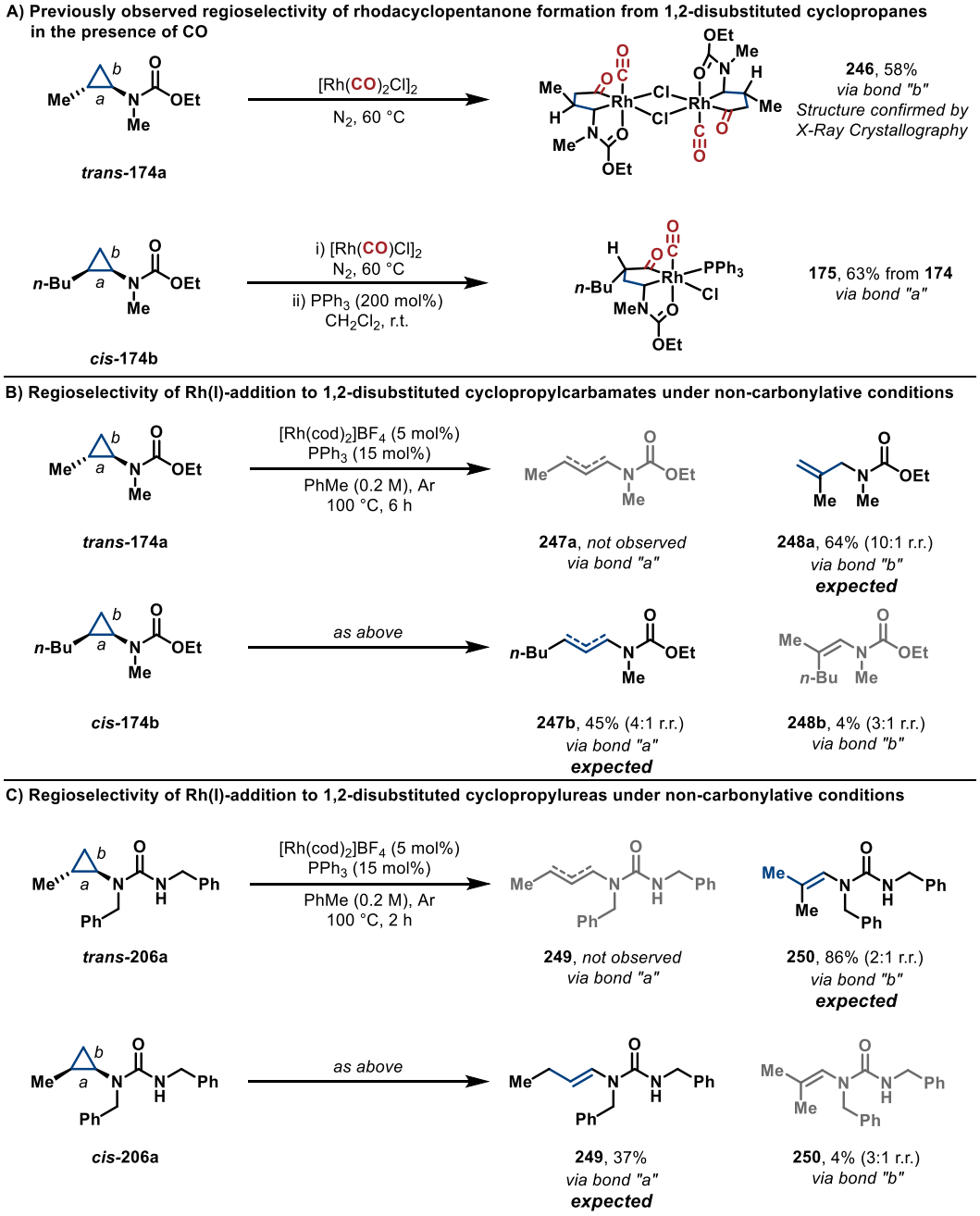
2.1.4.2 Regioselectivity of the (6+1) carbonylative cyclisation of 1,2-disubstituted cyclopropanes

McCreanor's studies and those presented in Section 2.1.3, involving the (6+1) carbonylative cyclisation of *trans*- and *cis*-1,2-disubstituted cyclopropylureas, demonstrate product regioselectivities which are opposite to that expected based on prior work carried out at Bristol (see Section 1.3.3). *Trans*-1,2-disubstituted cyclopropanes were expected to react *via* Rh(I)-addition to the least sterically hindered C-C bond "*b*", but were observed to react *via* the more hindered C-C bond "*a*" (Scheme 53). Furthermore, *cis*-1,2-disubstituted cyclopropanes were expected to react *via* the more sterically hindered bond "*a*", but were observed to react *via* the less hindered bond "*b*". Mechanistic studies were carried out to investigate the reasons for the unexpected regioselectivity.



Scheme 53: Unexpected regioselectivity of the (6+1) carbonylative cyclisation of 1,2-disubstituted cyclopropylureas.

Previously, Shaw investigated the regioselectivity of Rh(I)-addition to 1,2-disubstituted cyclopropanes in the presence of CO by generating stable rhodacyclopentanones.[101-102] *Trans*-cyclopropylcarbamate ***trans*-174a** formed complex **246** by Rh(I)-addition to the less hindered C-C bond "*b*" whereas *cis*-cyclopropylcarbamate ***cis*-174b** formed complex **175** by Rh(I)-addition to the more-hindered bond "*a*" (Scheme 54A). Then, insertion experiments (in the absence of CO) were carried out on the same cyclopropylcarbamates to confirm that the presence of CO did not influence the regioselectivity of Rh(I)-addition (Scheme 54B). In the event, *trans*-cyclopropylcarbamate ***trans*-174a** formed branched alkene **248a** in 64% yield *via* insertion into expected C-C bond "*b*". *Cis*-cyclopropylcarbamate ***cis*-174b** formed linear alkene **247b** in 45% yield *via* insertion into expected C-C bond "*a*" along with 4% of branched isomer **248b**. These results confirm that CO does not influence the regioselectivity of the C-C insertion step.

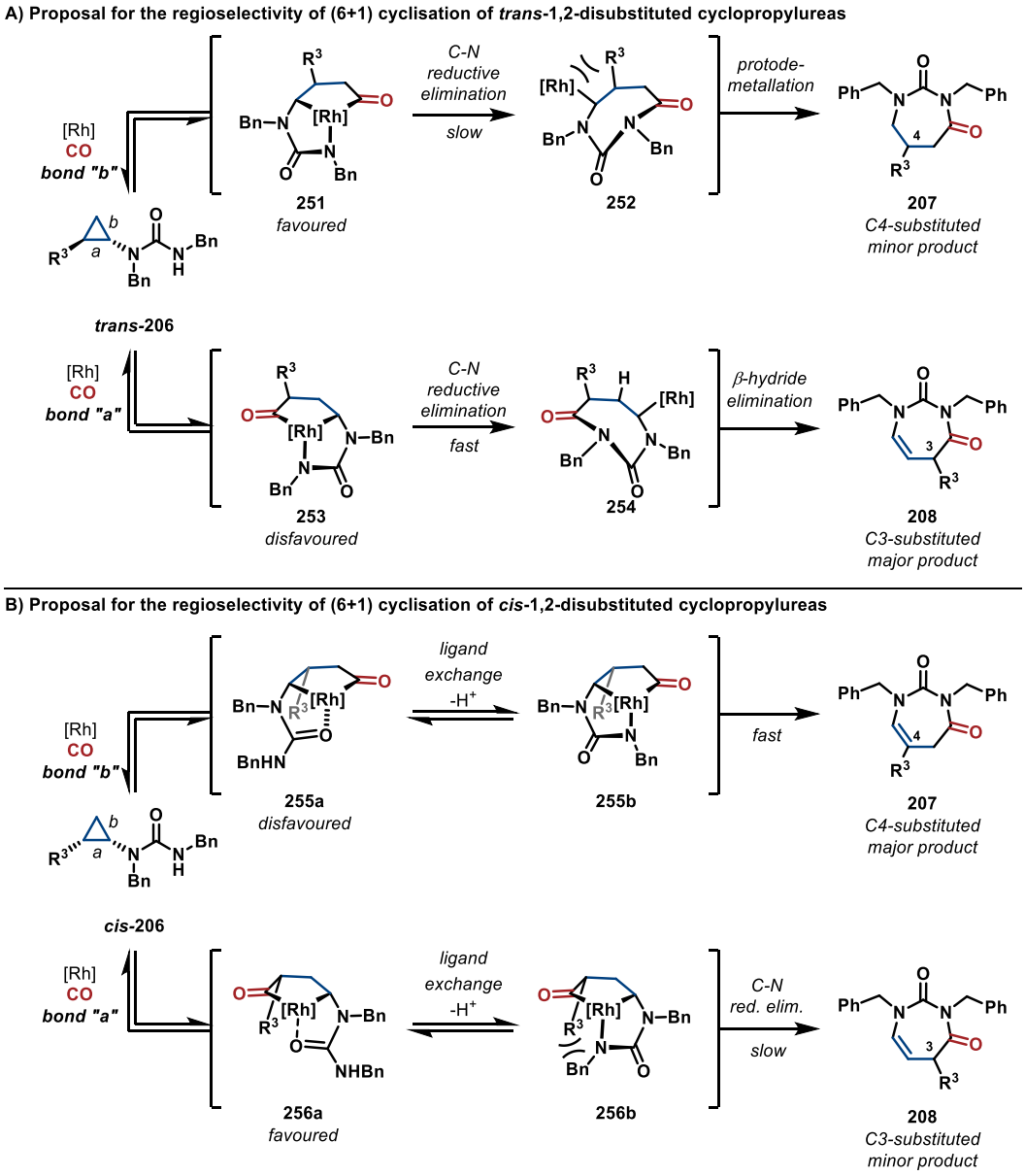


Scheme 54

Next, insertion experiments were performed on *trans*- and *cis*-1,2-disubstituted cyclopropyl*ureas*, ***trans*-206a** and ***cis*-206a**, to determine whether the urea directing group influenced the regioselectivity of Rh(I)-addition (Scheme 54C). In the absence of CO, *trans*-cyclopropylurea ***trans*-206a** provided branched alkene **250** in 86% yield *via* insertion into the expected bond "*b*". When *cis*-cyclopropane ***cis*-206a** was subjected to the same conditions, linear alkene **249** was formed in 37% yield along with 4% of the branched regioisomer. Both of these results are in accordance with the previously reports and are in contrast to the regioselectivity of the (6+1) carbonylative cyclisation of cyclopropylureas observed by McCreanor and in Section 2.1.3. Therefore, it was concluded that product regioselectivity in the (6+1) carbonylative cyclisation of 1,2-disubstituted cyclopropane substrates is

not a result of the urea directing group, but might be a *result of reversible rhodacyclopentanone formation*, whereby the selectivity is determined by a process other than the initial C-C oxidative addition step.

A model for the observed regioselectivity of *trans*-cyclopropylureas is proposed in Scheme 55A. Based on previous studies, *trans*-cyclopropylureas ***trans*-206** favours formation of rhodacyclopentanone **251** *via* Rh(I)-addition to C-C bond "*b*". However, C-N reductive elimination to form intermediate **252** is slow due to a developing steric clash between the [Rh]-centre and R^3-substituent. Rhodacyclopentanone **251** therefore reverts to *trans*-cyclopropylureas ***trans*-206** by retro-carbonylation and C-C reductive elimination. Under equilibrium the disfavoured rhodacyclopentanone **253** forms *via* Rh(I)-addition to hindered C-C bond "*a*" of cyclopropane ***trans*-206**. C-N Reductive



Scheme 55

elimination from intermediate **253** is fast because of the less demanding 1,3-relationship between the [Rh]-centre and R^3-substituent of diazepane **254**. β-Hydride elimination from diazepane **254** provides C3-substituted diazepane **208**. In cases where R^1 = H, low regioselectivity is observed (see Table 7). This might be explained by considering the formation of corresponding intermediate **252** where the developing steric clash between the [Rh]-centre and R^3-substituent is alleviated by the presence of a small R^1-substituent (R^1 = H).

A related argument for the selective formation of C4-substituted diazepanes from *cis*-1,2-disubstituted cyclopropylureas is illustrated in Scheme 55B. Rhodacyclopentanone **256a** is formed by favourable Rh(I)-addition to the more electron-rich bond "*a*" of *cis*-cyclopropylurea ***cis*-206** and ligand exchange forms **256b**. However, C-N reductive elimination from **256b** is accompanied by a developing steric clash between the R^2- and R^3-substituents (shown on **256b**). As a result, reversible rhodacyclopentanone formation allows equilibration to disfavoured rhodacyclopentanone **255a** from which ligand exchange and all proceeding steps are facile, resulting in the selective formation of C4-substituted diazepanes. Thus, the observed regioselectivity of the (6+1) carbonylative cyclisation is determined by the ease of C-N reductive elimination and not by Rh(I)-addition to the cyclopropane.

2.1.5 Conclusion

Building on McCreanor's discovery, the (6+1) carbonylative cyclisation of cyclopropylureas to form 1,3-diazepanes in which the key step is the nucleophilic addition of a *N*-nucleophile to a rhodacyclopentanone, was developed. The optimised conditions allowed the efficient cyclisation of diverse trisubstituted and *N*,*N*'-disubstituted cyclopropylureas including multiple classes of substituted cyclopropane. Furthermore, the oxidation level of the C4-C5 position of the product diazepanes could be controlled by the choice of the R^1-substituent. The regioselectivity observed when 1,2-disubstituted cyclopropanes were employed was controlled by the C-N reductive elimination step and not by the initial C-C insertion step as in previous methodologies from the group. This preliminary example serves as a proof-of-concept for a broader strategy for the formation of medium-sized rings by the intramolecular nucleophilic trapping of rhodacyclopentanones.

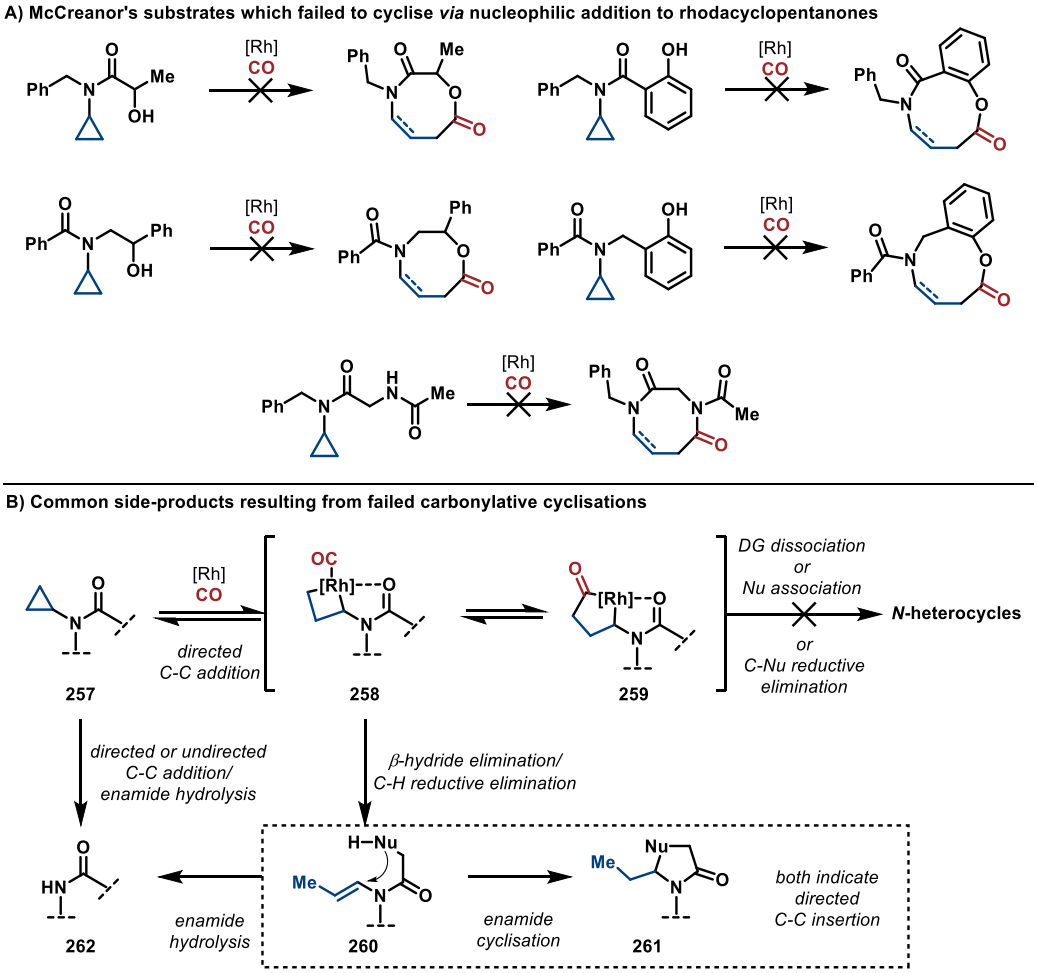
2.2 Further investigations into intramolecular nucleophilic addition to rhodacyclopentanones

The (6+1) carbonylative cyclisation of cyclopropylureas, described in Section 2.1, served as a proof of concept for a strategy for the formation of seven-membered, or larger heterocycles by intramolecular nucleophilic addition to rhodacyclopentanones. Subsequently, the generality of this process was investigated with the aim of identifying a second intramolecular protocol and gaining further insight into the factors governing the success of the cyclisation.

2.2.1 Prior studies carried out by McCreanor

Prior to the discovery of the (6+1) carbonylative cyclisation of cyclopropylureas, McCreanor investigated several intramolecular systems that failed to undergo the desired carbonylative cyclisation (Scheme 56A). Notably, all the substrates were aminocyclopropane derivatives equipped with an amide directing group. Amides had previously been measured (by the CO stretching frequency of model rhodacyclopentanones, Section 1.3.1) to be weaker directing groups than carbamates and ureas, and were less effective in previous carbonylative cyclisations (Section 1.3.2). Furthermore, McCreanor investigated a narrow selection of nucleophiles (alcohols, phenols and an amide) most of which had been successful in the intermolecular protocol (Section 1.4.1).

During his investigations, McCreanor identified several side-products, which provide information regarding the problematic steps in the proposed catalytic cycles (Scheme 56B). For example, under Rh(I)-catalysed carbonylative conditions, several of the substrates shown in Scheme 56A formed linear alkenes **260**, or linear alkene adducts **261** (formed by intramolecular nucleophilic addition to the corresponding alkene). Linear alkenes **260** are formed by Rh(I)-addition to the *proximal* cyclopropyl C-C bond of aminocyclopropanes **257** and degradation of the resulting rhodacyclobutanes **258** (*via* a similar mechanism to the insertion experiments discussed in Section 1.3.1). It has previously been mentioned that rhodacyclobutanes **258** are rapidly and reversibly converted to rhodacyclopentanones **259** in the presence of CO. Therefore, the formation of linear alkenes **260** (or alkene adducts **261**) is considered indirect proof that the desired rhodacyclopentanone was formed, and consequently that one of the proceeding catalytic steps (directing group dissociation, nucleophile association, deprotonation or C-Nu reductive elimination) had failed. McCreanor also observed the formation of decyclopropanated side-products **262**, which are formed by either directed or undirected Rh(I)-addition to the cyclopropane and hydrolysis of the resulting alkene. Therefore, decyclopropanated side-products are not an indication that Rh(I)-addition was directed.



Scheme 56

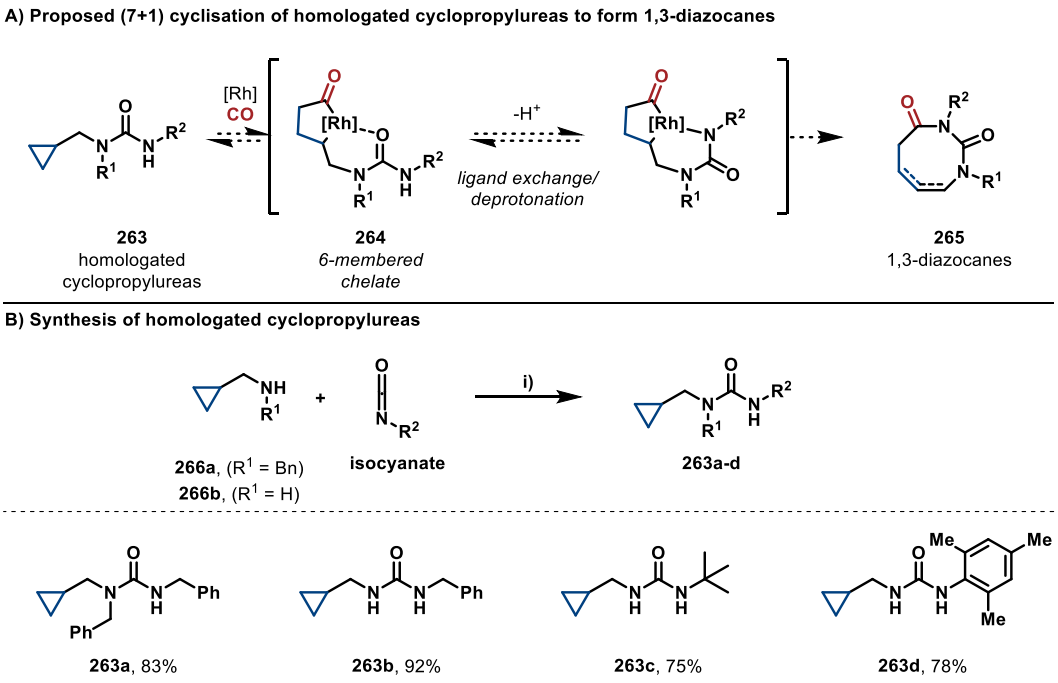
2.2.2 Attempts to identify a second intramolecular protocol

In order to investigate the generality of the nucleophilic cyclisation strategy outlined in Scheme 37, several cyclopropane-based substrates were designed and tested. In the course of these investigations, the three main components of a cyclisation substrate (the cyclopropane, directing group and nucleophile) were varied. Typically, each substrate was reacted under several carbonylation conditions, which included a cationic Rh(I)-catalyst ([Rh(cod)$_2$]BARF, [Rh(cod)$_2$]BF$_4$, or [Rh(cod)$_2$]OTf), triarylphosphine ligand (typically PPh$_3$ or P(3,5-bis(CF$_3$)C$_6$H$_3$)$_3$) and solvent (typically 1,2-DCB or benzonitrile), in accordance with previous studies. Each reaction was run under a balloon-pressure of CO and heated between 100–150 °C (or higher if little reactivity is observed) for at least 16 hours.

2.2.2.1 Homologated-cyclopropylureas

The success of the (6+1) carbonylative cyclisation of cyclopropylureas prompted investigations into homologated system **263**, which upon cyclisation would form 1,3-diazocanes **265** (Scheme 57A).

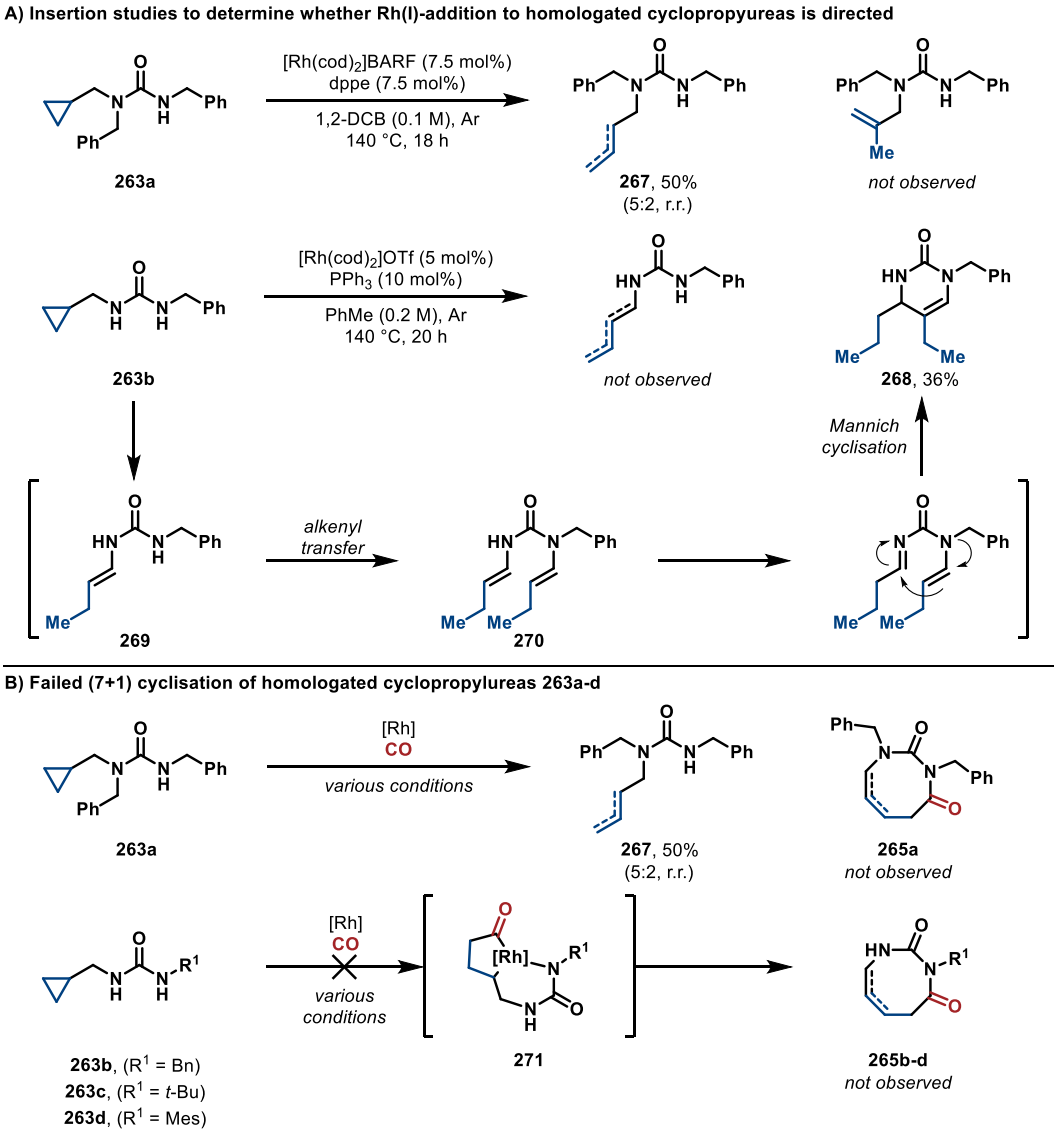
Here, an "electron-neutral" cyclopropylmethyl moiety is employed instead of an "electron-rich" aminocyclopropane. In general, electron-rich cyclopropanes are more susceptible to Rh(I)-addition than electron-deficient analogues.[106,159] Furthermore, the additional methylene unit between the cyclopropane and directing group requires a six-membered chelate between the rhodacyclopentanone and directing group (see intermediate **264**), which might hinder directed C-C oxidative addition. In order to investigate this proposal, trisubstituted cyclopropylmethylureas **263a** and *N*,*N*'-disubstituted ureas **263b-d** were synthesised in excellent yields (75–92%) by reacting the corresponding cyclopropylmethylamine (**266a** or **266b**) with the desired isocyanate (Scheme 57B).



Scheme 57: A) *Reagents and conditions*: i) NEt_3, CH_2Cl_2, r.t., 2 h.

Initially, insertion experiments were conducted on trisubstituted urea **263a** and *N*,*N*'-disubstituted urea **263b** to determine whether directed Rh(I)-addition to the homologated cyclopropane was feasible (Scheme 58A). In the absence of CO, trisubstituted urea **263a** underwent directed Rh(I)-addition to form linear alkenes **267** in 50% yield, and none of the branched alkene was observed. Under identical conditions, *N*,*N*'-disubstituted urea **263b** reacted to form cyclic urea **268** in 36% yield. Cyclic urea **268** is proposed to have formed by initial formation of linear alkene **269** (not observed). Transfer of the alkenyl fragment from one equivalent of alkene **269** to another equivalent of **269** could form dialkenyl species **270**, which could undergo an intramolecular Mannich-type cyclisation to form **268**. The formation of linear alkenes **267** and cyclic urea **268** indicate that Rh(I)-addition to the homologated cyclopropane of substrates **263a** and **263b** is directed, which set the stage for subsequent investigations into the carbonylative cyclisation of homologated cyclopropylureas.

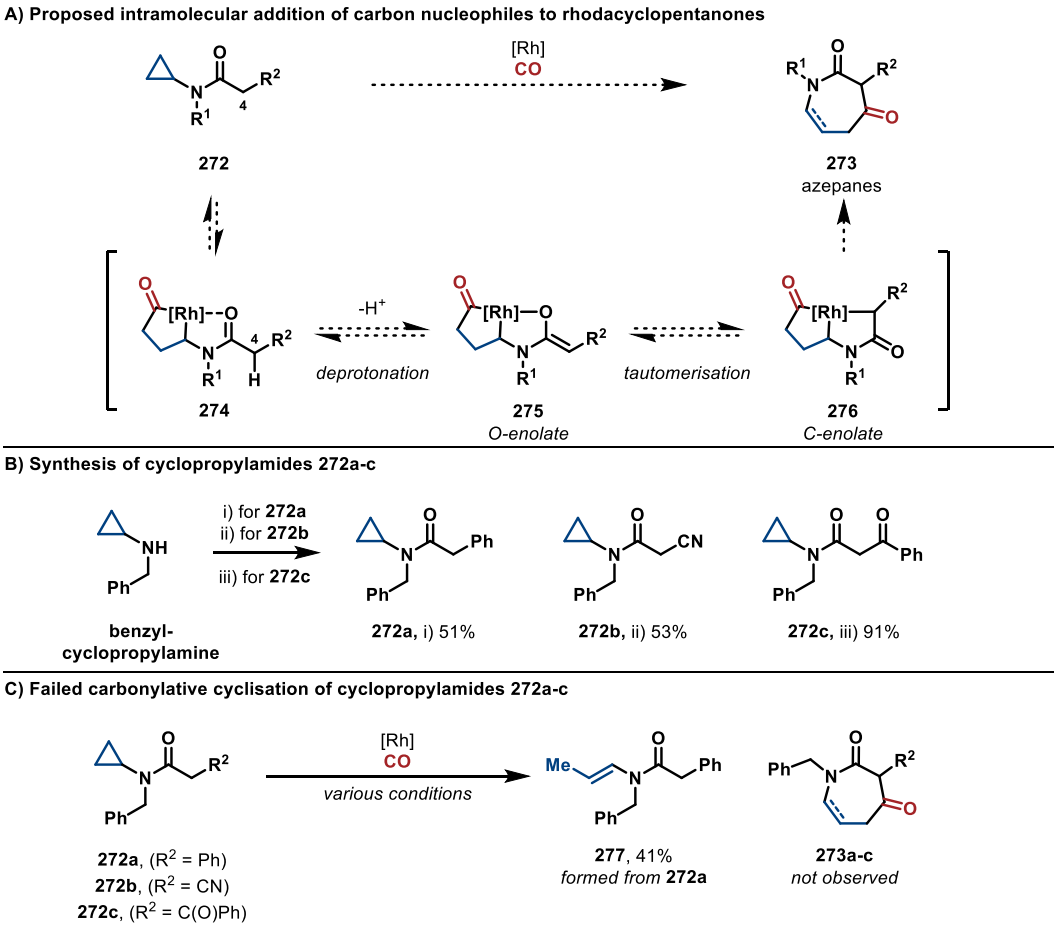
Next, homologated ureas **263a-d** were reacted under carbonylative cyclisation conditions (Scheme 58B). Initially, trisubstituted urea **263a** was treated with various combinations of cationic Rh(I)-catalysts and mono-/bidentate phosphine ligands in the non-coordinating solvent 1,2-DCB, which resulted in the formation of linear alkenes **267** (50%) and none of the desired product **265a**. Similarly, when *N*,*N*'-disubstituted urea **263b** was subjected to carbonylative conditions, the desired diazocane **265b** was not observed. The formation of linear alkenes **267** from the reaction of trisubstituted urea **263a** indicates that the rhodacyclopentanone was being formed, but that one of the following steps failed. Therefore, bulky disubstituted ureas **263c** and **263d** were reacted under identical conditions in the hope that the large R^2-substituents (*t*-Bu and mesityl) would promote C-N reductive elimination from rhodacyclopentanones **271**.[158] In the event, both homologated cyclopropylureas failed to form the corresponding (7+1) carbonylative cyclisation products **265c** or **265d**. At this point, investigations into the homologated cyclopropylureas were paused in favour of alternative systems.



Scheme 58

2.2.2.2 Carbon nucleophiles

Up until this point, only a narrow range of *O*- and *N*-based functional groups had been investigated as nucleophiles for addition to rhodacyclopentanones, and so alternative nucleophilic functional groups were considered. This led to the identification of enolates as potential *C*-based nucleophiles because enolates are known to undergo transmetallation with various transition metals, including rhodium, to form transition metal enolates.[160-161] In order to investigate the feasibility of enolate addition to rhodacyclopentanones, cyclopropylamides **272**, which contain enolisable C4-positions, were designed (Scheme 59A). The cyclisation of cyclopropylamides **272** was proposed to begin with amide-directed formation of rhodacyclopentanone **274**. Deprotonation of the C4-position of rhodacyclopentanone **274** would be facilitated by coordination to the Rh(III)-species, resulting in the formation of *O*-bound Rh(III)-enolate **275**. Tautomerisation to *C*-bound Rh(III)-enolate **276** and C-C reductive elimination would ultimately form azepanes **273**.

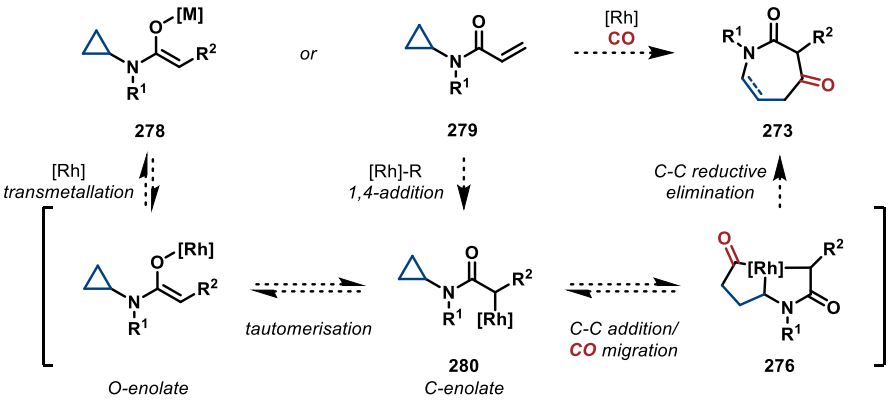


Scheme 59: B) *Reagents and conditions*: i) phenylacetyl chloride, NEt_3, CH_2Cl_2, 0 °C, 4 h; ii) cyanoacetic acid, DCC, DMAP, CH_2Cl_2, 0 °C to r.t., 4 h; iii) ethyl benzoylacetate, DMAP, PhMe, reflux, 18 h.

To test the hypothesis in Scheme 59A, cyclopropylamides **272a-c** were synthesised with different anion-stabilising R^2-substituents, in order to test nucleophilic C4-positions with a range of

pK_as (Scheme 59B). Phenyl derivative **272a** was prepared by coupling benzylcyclopropylamine with phenylacetyl chloride in 51% yield. Cyano-derivative **272b** was accessed by DCC-coupling of benzylcyclopropylamine and cyanoacetic acid in 53% yield, and dicarbonyl substrate **272c** was formed in 91% yield by reacting benzylcyclopropylamine with ethyl benzoylacetate in the presence of DMAP.

Cyclopropylamides **272a-c** were then exposed to a range of carbonylative cyclisation conditions. Phenyl derivative **272a** underwent Rh(I)-addition to form linear alkenes **277** in 41% yield, but did not provide the desired azepane **273a** (Scheme 59C). The formation of linear alkene **277** suggested that rhodacyclopentanone **274** was formed, but enolate addition did not take place. Therefore, several inorganic bases ($NaHCO_3$, $CsCO_3$, KH_2PO_4) were included in the reaction to promote deprotonation of the C4-position, but this hindered Rh(I)-addition to the cyclopropane such that substrate **272a** remained unreacted. Additionally, substrates **272b** and **272c**, bearing more acidic C4-positions, also failed to form the desired azepanes under carbonylative cyclisation conditions. The apparent difficulty in accessing intermediate Rh(III)-enolates **275**/**276** appeared to hinder carbonylative cyclisation. This difficulty could be circumvented by forming the Rh(III)-enolates *via* a different order of catalytic steps. For example, *C*-bound Rh(I)-enolate **276** might be accessed by transmetallation of a preformed metal enolate **278**,[160, 162-163] or by 1,4-addition of a Rh(I)-species to cyclopropylacrylamide **279** (Scheme 60). Resulting *C*-bound Rh(I)-enolate **280** formed in each case might undergo intramolecular Rh(I)-addition to the proximal cyclopropane C-C bond and carbonylation to provide an alternative entry to rhodacyclopentanone **276**. These proposals were not investigated at this stage.

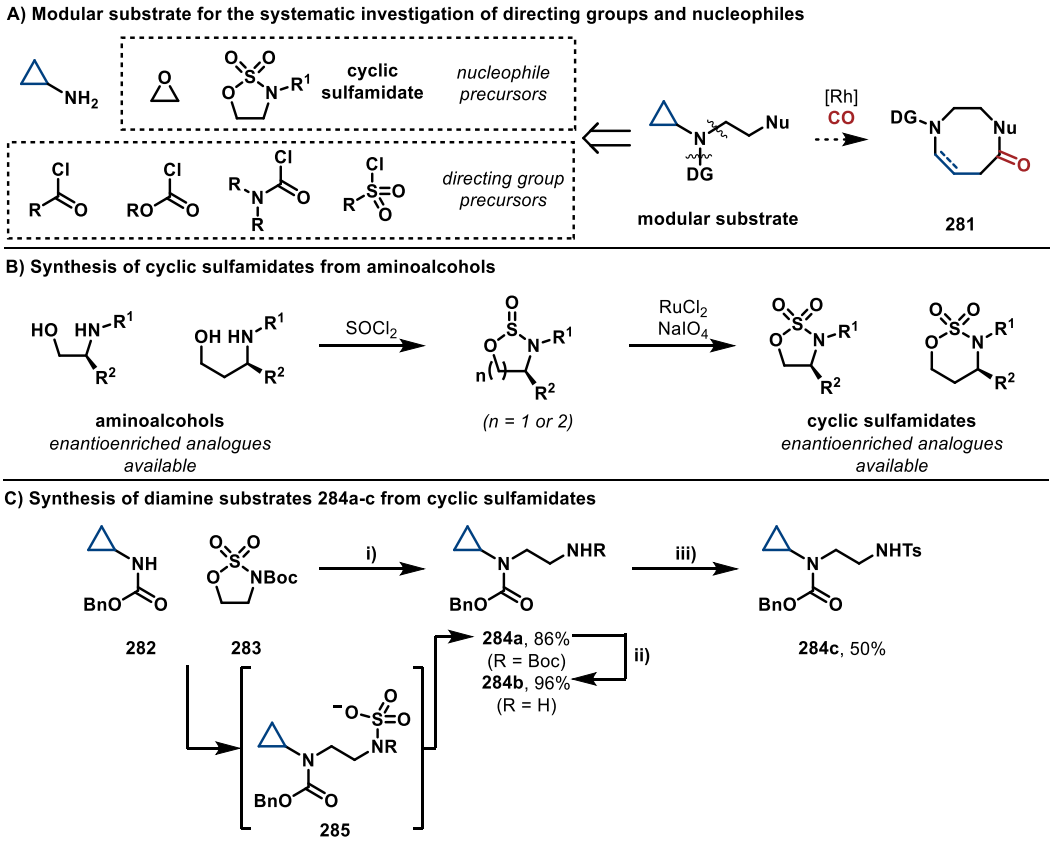


Scheme 60: Alternative entry to rhodacyclopentanone **276** *via* initial formation of a Rh(I)-enolate.

2.2.2.3 Modular substrates for systematic investigations

In the two systems described so far (Scheme 58 and 59), linear alkenes were the only discernible side-products of the attempted carbonylative cyclisation, which indicated that one of the steps after rhodacyclopentanone formation failed. Aside from the evidence provided by linear alkenes, no information regarding the problematic catalytic step could be derived because the cyclisation systems were significantly different. Therefore, a modular substrate was designed to allow each of the basic

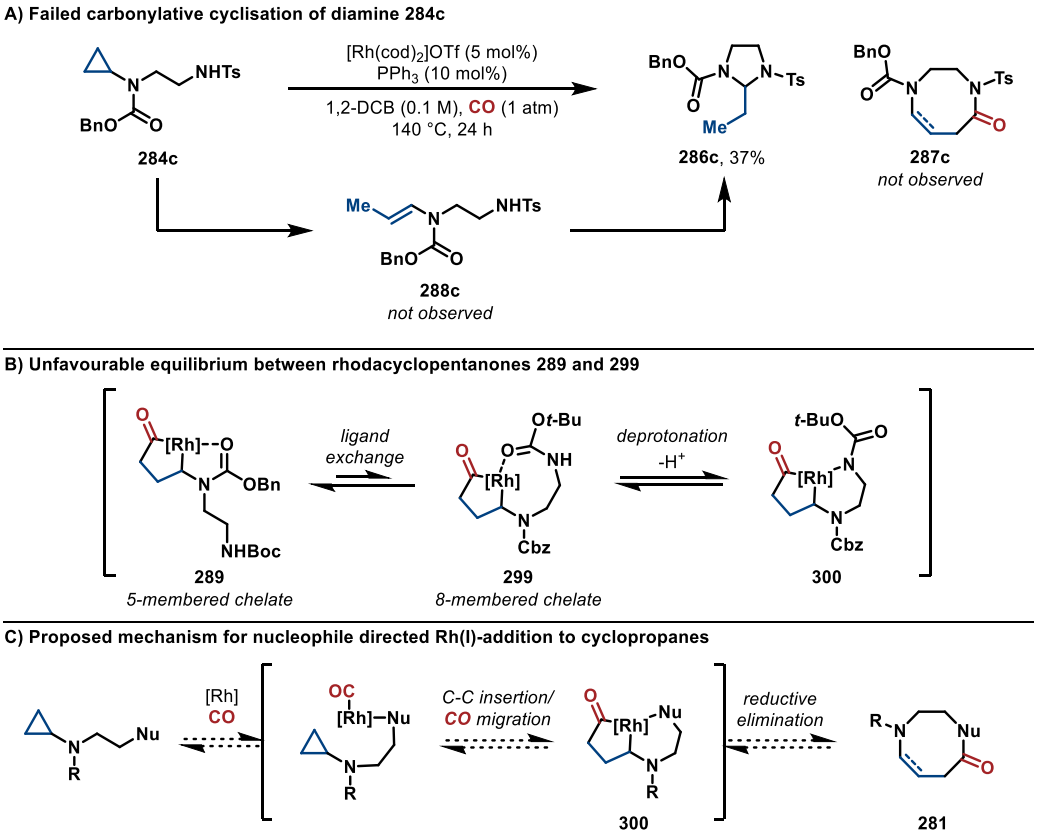
substrate components (cyclopropane, directing group and nucleophile) to be independently varied, thereby allowing a systematic study of the factors affecting cyclisation to form eight-membered heterocycles **281** (Scheme 61A). Key to this proposal was the use of a modular substrate, which could be prepared from a pool of electronically diverse nucleophile and directing group precursors. Cyclic sulfamidates were identified as particularly useful nucleophile precursors because these allowed the electronic properties of the nucleophile to be tuned through the choice of protecting group (PG) (Scheme 61B).[164] Additionally, cyclic sulfamidates are readily prepared from aminoalcohols of which many chiral analogues are commercially available.



Scheme 61: C) *Reagents and conditions*: i) NaH, DMF, 30 min, r.t. *then* 2 M HCl, r.t., 30 min; ii) TFA, CH_2Cl_2, r.t., 1 h; iii) TsCl, NEt_3, CH_2Cl_2, 0 °C to r.t., 16 h.

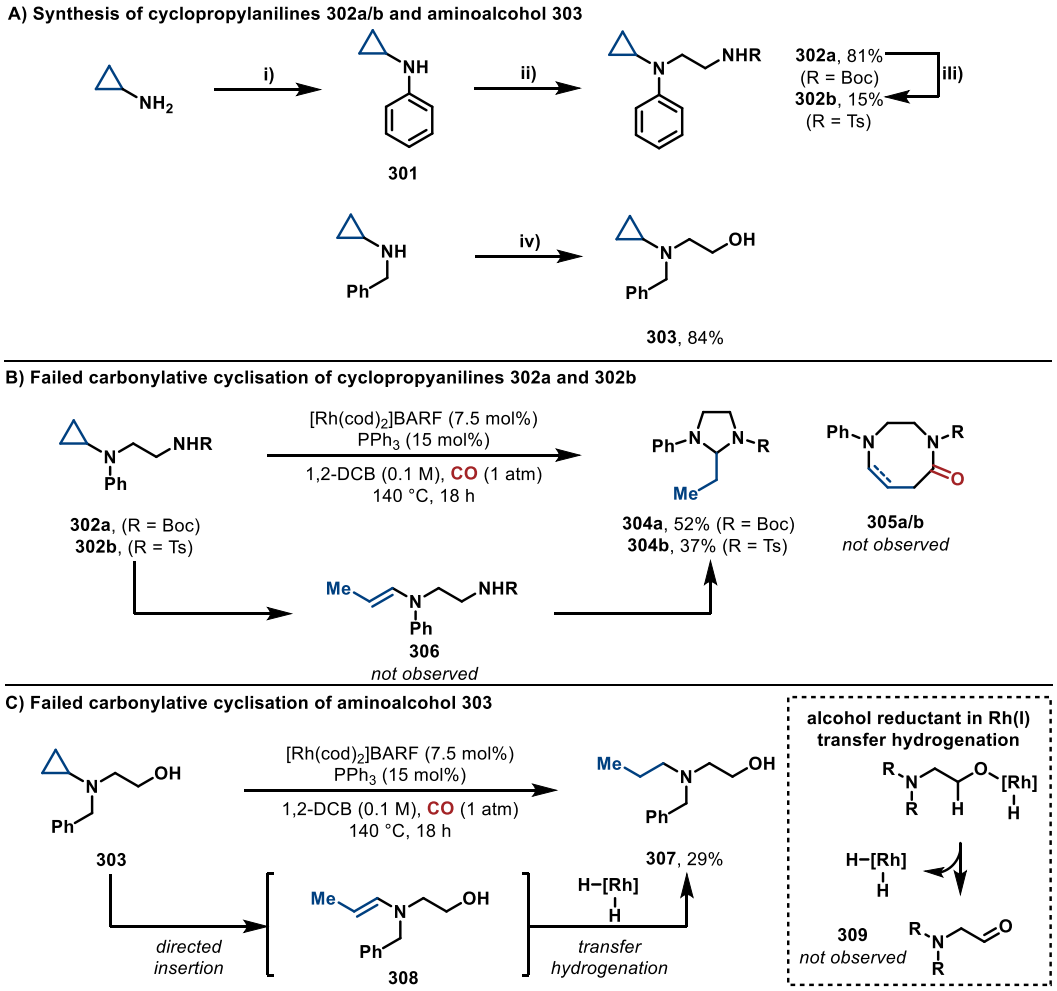
Experiments began with the synthesis of cyclopropylcarbamates **284a-c** bearing a carbamate directing group and electronically differentiated *N*-nucleophiles (Scheme 61C). Cyclopropylcarbamate **282** was deprotonated with NaH in DMF and treated with Boc-protected sulfamidate **283**, which provided substrate **284a** in 86% yield upon hydrolysis of intermediate **285**. Boc-deprotection with trifluoroacetic acid proceeded to form primary amine **284b** in 96% yield, which was then reacted with *p*-toluenesulfonyl chloride to form sulfonamide **284c** in 50% yield. Using cyclic sulfamidate **283**, three potential cyclisation substrates (**284a-c**) were synthesised in only five steps.

Cyclopropylcarbamates **284a-c** were subjected to several carbonylative cyclisation conditions, but desired diazepanes **287a-c** were not observed (Scheme 62A). When *N*-tosyl substrate **284c** was reacted, imidazolidine **286b** was formed in 37% yield by intramolecular cyclisation of linear alkene **288c**, again suggesting that the cyclisation failed to proceed past the formation of the rhodacyclopentanone. It was considered that the proposed equilibrium between five-membered chelate **289** and eight-membered chelate **299** would significantly favour the smaller of the two, thereby restricting coordination of the nucleophile to the Rh(III)-centre (Scheme 62B). A solution to this problem was envisaged in which the nucleophile also acts as a directing group for Rh(I)-addition to the cyclopropane. If successful, rhodacyclopentanone **300** would be formed thus avoiding a ligand exchange step (Scheme 62C).



Scheme 62

In order to test the hypothesis in Scheme 62C, cyclopropylanilines **302a** and **302b**, and aminoalcohol **303** were prepared (Scheme 63A). Cyclopropylaniline **301** was prepared by a Buchwald-Hartwig amination with cyclopropylamine before being deprotonated with *n*-BuLi and reacted with Boc-sulfamidate **283**, which resulted in the smooth formation of Boc-amine **302a** in 81% yield. Boc-deprotection and tosylation then provided tosylamine **302b** in 15% yield over two steps. Aminoalcohol **303** was prepared in 84% yield by $ZnCl_2$-mediated nucleophilic ring-opening of ethylene oxide.



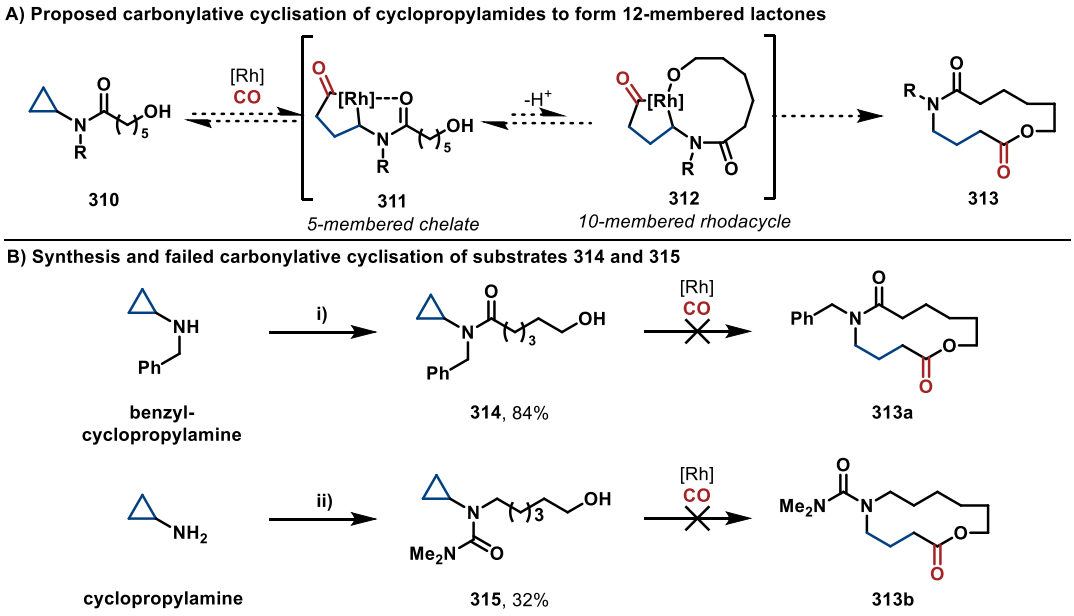
Scheme 63: A) *Reagents and conditions*: i) bromobenzene, Pd_2dba_3, BINAP, sodium pentoxide, PhMe, 130 °C, 16 h; ii) **283**, *n*-BuLi, THF, 30 min, r.t. *then* aq. 2 M HCl, 30 min; iii) TFA, CH_2Cl_2, 0 °C to r.t. *then* TsCl, NEt_3, CH_2Cl_2, 0 °C to r.t., 16 h; iv) ethylene oxide, $ZnCl_2$, THF, r.t., 19 h.

The attempted cyclisation of cyclopropylanilines **302a** and **302b** did not form desired diazocanes **305a/b**, but did provide imidazolidines **304a** (52% from **302a**) and **304b** (37% from **302b**) (Scheme 63B). The formation of imidazolidines (presumably *via* linear alkenes **306**) is an indication that Rh(I)-addition was directed by the nucleophile. When aminoalcohol **303** was reacted under carbonylative cyclisation conditions, linear *alkane* **307** was formed as the sole discernible product in 29% yield (Scheme 63C). Linear alkane **307** is likely the product of reduction of linear alkene **308** by a Rh(III)-mediated transfer hydrogenation mechanism. Here, an alcohol would serve as a reductant forming aldehyde side-products **309** although these were not observed. Similar Rh(III)-catalysed transfer hydrogenations are known.[165] Nevertheless, the formation of imidazolidines **304a** and **304b**, and linear alkane **307** implies that the nucleophiles were successful in directing Rh(I)-addition to cyclopropanes, but that one of the following catalytic steps failed. Having failed to achieve a carbonylative cyclisation of various substrates based on the modular system described in Scheme 61A, studies were moved to another example. A more informative systematic evaluation of the components

of a successful nucleophilic trapping of rhodacyclopentanones would require the initial identification of a viable cyclisation substrate.

2.2.2.4 Substrates for the synthesis of larger ring systems

Medium-sized (defined as eight- to eleven-membered rings) cycloalkanes possess significant ring strain (approximate strain energy values of 9.4 kcal/mol for cyclooctane to 11.1 kcal/mol for cycloundecane[166]), which drops off substantially for twelve-membered rings (approximate strain energy values of 4.0 kcal/mol for cyclododecane[166]). In terms of lactones, the drop off in ring strain occurs on going from simple nine-membered lactones (approximate strain energy value of 11.6 kcal/mol[167]) to ten-membered lactones (approximate strain energy value of 8.2 kcal/mol[167]). Analysis of these values led Galli and Mandolini to conclude that the ring strain of the cyclisation product was a factor in their formation from linear substrates.[148] Therefore, reductive elimination from rhodacyclopentanones to form medium-sized rings must be sufficiently exergonic to incorporate the ring strain of the product heterocycle, and this might have been a factor in the failed carbonylative cyclisations discussed so far.



Scheme 64: B) *Reagents and conditions*: i) 6-hydroxyhexanoic acid, EDCI, DMAP, CH_2Cl_2, 0 °C to r.t., 16 h; ii) 6-bromohexan-1-ol, MeCN, 80 °C, 6 h *then* dimethylcarbamoyl chloride, NEt_3, CH_2Cl_2, 0 °C, 3 h.

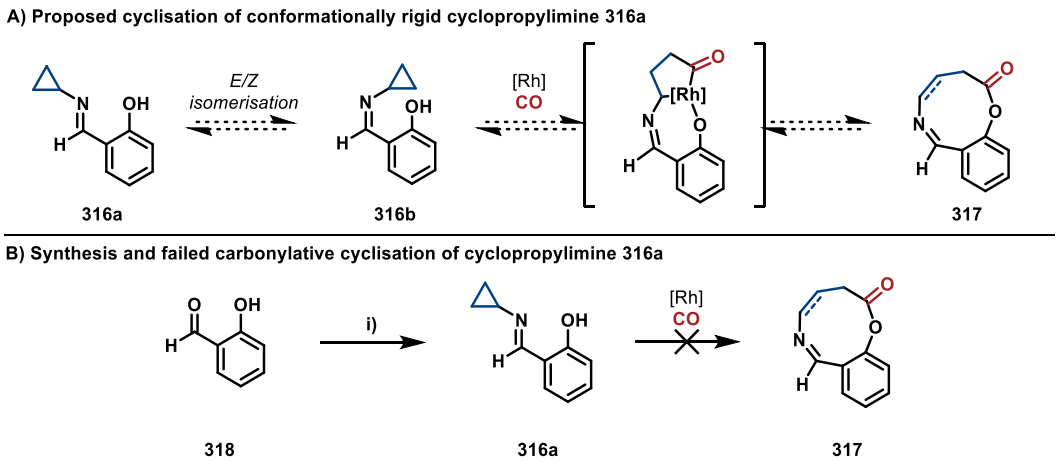
With this in mind, investigations were directed towards the formation of less strained twelve-membered ring systems by cyclisation of substrates **310** bearing long nucleophile tethers (Scheme 64A). The proposed mechanism of cyclisation involves initial formation of rhodacyclopentanone **311** followed by ligand exchange between the directing group and nucleophile. Reductive elimination from rhodacycle **312** would form twelve-membered lactones **313**. Presumably, the use of a long nucleophile tether disfavours equilibration from five-membered chelate **311** to 10-membered rhodacycle **312** thereby inhibiting cyclisation. Nevertheless, substrates **314** and **315** were targeted (Scheme 64B). Ester

substrate **314** was formed in 84% yield, by EDCI-coupling of cyclopropylamine with 6-hydroxyhexanoic acid. Urea substrate **315** was formed in 32% yield by a one-pot procedure involving initial alkylation of cyclopropylamine with 6-bromohexan-1-ol, followed by urea formation with dimethylcarbamoyl chloride. Unfortunately, when cyclisation substrates **314** and **315** were subjected to carbonylative cyclisation, neither of the desired twelve-membered lactones **313a** nor **313b** were observed.

2.2.2.5 Conformationally restricted nucleophiles

The investigatory systems discussed in the previous section employed nucleophiles with a high degree of conformational flexibility between the cyclopropane and nucleophile. Presumably, too much conformational flexibility may hinder carbonylative cyclisation by imposing a kinetic barrier to nucleophilic addition to the rhodacyclopentanone. Therefore, substrates with a high degree of preorganisation were designed wherein the nucleophile was attached to the cyclopropane portion *via* conformationally rigid tethers.

Firstly, cyclopropylimine **316a** was targeted in which the cyclopropane and phenol nucleophile are connected by a rigid framework of sp^2-hybridised carbon atoms (Scheme 65A). Here, cyclopropylimine **316a** would presumably exist in the *E*-configuration, so isomerisation to *Z*-imine **316b** must take place under the reaction conditions prior to Rh(I)-addition. Phenol-directed rhodacyclopentanone formation and C-O reductive elimination would then provide benzolactone **317**. Initially, cyclopropylimine **316a** was synthesised in 97% yield by mixing benzaldehyde **318** and cyclopropylamine (Scheme 65B) in ethanol. Unfortunately, when subjected to various Rh(I)-catalysed carbonylative cyclisation conditions, imine **316** did not react to give the desired benzolactone **317**.

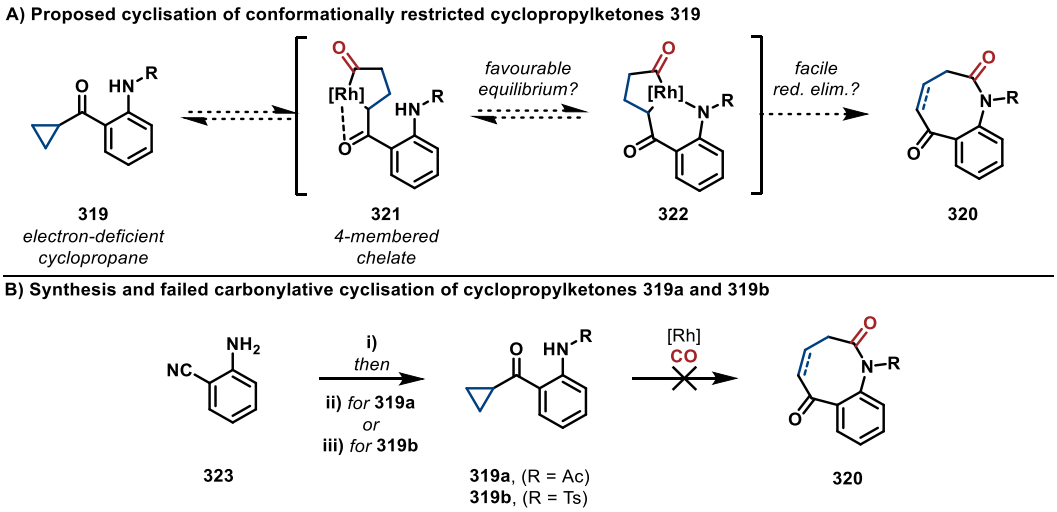


Scheme 65: B) *Reagents and conditions*: i) cyclopropylamine, EtOH, r.t., 16 h.

Next, cyclopropylketones **319** was targeted as a second class of cyclisation substrate exhibiting a large degree of preorganisation (Scheme 66A). In this case, ketone-directed rhodacyclopentanone

formation would provide rhodacyclopentanone **321**. Nucleophilic addition of the *N*-aryl nucleophile to rhodacyclopentanone **321** and C-N reductive elimination would form benzolactams **320**. This substrate class posed several issues. For example, cyclopropylketones are challenging substrates because ketones are weak directing groups and Rh(I)-addition to electron-deficient cyclopropanes is challenging.[159] Conversely, the weak four-membered chelate in intermediate **321** might favour coordination of the *N*-nucleophile to the Rh(III)-centre (as in **322**). Furthermore, the highly electron-deficient rhodacyclopentanone **322** (due to the electron-withdrawing effect of the ketone) might undergo facile C-N reductive elimination to form benzolactams **320**.

Investigations began with the synthesis of cyclopropylketones **319a** and **319b**, which contained different *N*-protecting groups (Scheme 66B). The synthesis began with nucleophilic addition of cyclopropylmagnesium bromide onto benzonitrile **323**, which formed the unsubstituted aniline (not shown) in 28% yield upon imine hydrolysis during the work-up. Substrates **319a** and **319b** were prepared by reaction of the aniline functionality with AcCl (75% yield for **319a**) and *p*-toluenesulfonyl chloride (50% yield for **319b**), respectively. When subjected to various Rh(I)-catalysed carbonylative cyclisation conditions, both substrates proved extremely resistant to C-C oxidative insertion, even at elevated temperatures of 170 °C. Subsequent work carried out at Bristol has identified an efficient catalyst system for Rh(I)-addition to electron-deficient cyclopropanes, which may be applicable in the current reaction.[159]

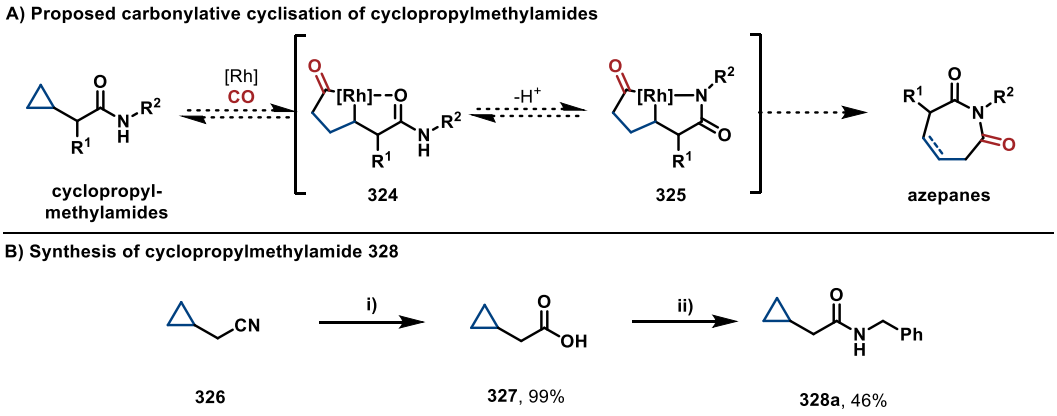


Scheme 66: B) *Reagents and conditions*: i) cyclopropylmagnesium bromide, THF, 0 °C, 6 h *then* aq. 2 M HCl, r.t., 28%; ii) AcCl, NEt_3, CH_2Cl_2, 0 °C, 3 h, 75%; iii) TsCl, NEt_3, CH_2Cl_2, 0 °C to r.t., 16 h, 50%.

2.2.2.6 Cyclopropylmethylamides

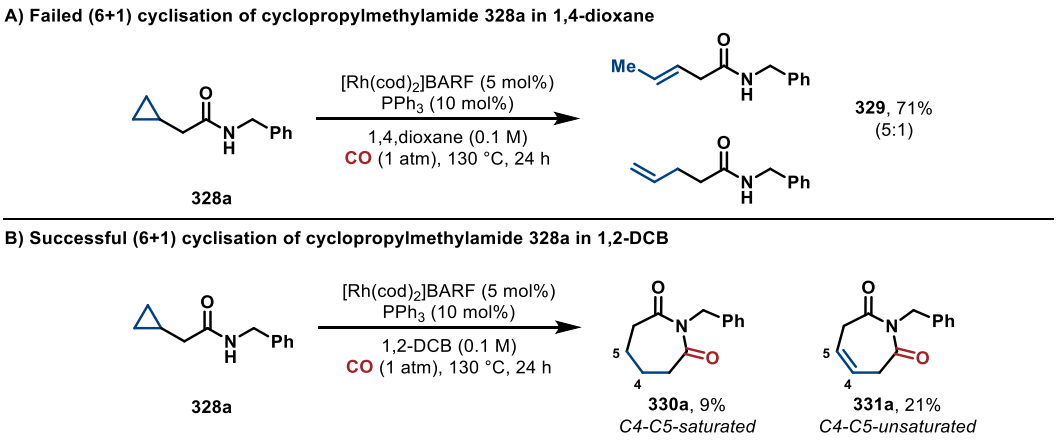
Following on from the studies involving electron-deficient cyclopropanes, discussed above and in Section 2.2.2.1, "electron-neutral" cyclopropanes were investigated in the carbonylative cyclisation. Cyclopropylmethylamides were designed as an analogue of the cyclopropylureas discussed in Section

2.1, which are electronically differentiated through the use of a weaker amide directing group and less-activated alkylcyclopropane (Scheme 67A). The proposed mechanism of cyclisation of cyclopropylmethylamides begins with amide-directed formation of rhodacyclopentanones **324** followed by ligand exchange with the nucleophile and concomitant deprotonation. C-N Reductive elimination from intermediates **325** would form azepanes. Cyclopropylmethylamide **328a** was initially targeted. Hydrolysis of cyclopropylacetonitrile **326** formed carboxylic acid **327** quantitatively, and then DCC-coupling with benzylamine provided cyclopropylmethylamide **328a** in 46% yield (Scheme 67B).



Scheme 67: A) *Reagents and conditions*: i) KOH, H_2O, reflux, 5 h; ii) benzylamine, DCC, DMAP, CH_2Cl_2, 0 °C to r.t., 2 h.

When cyclopropylmethylamide **328a** was treated with cationic $[Rh(cod)_2]BARF$ and PPh_3 in 1,4-dioxane under a carbonylative atmosphere linear alkenes **329** were formed in 71% yield, indicating that the amide directing group had directed C-C oxidative addition to the electron-neutral cyclopropane (Scheme 68A). Fortunately, when the reaction was run in 1,2-DCB under otherwise identical conditions, the desired C4-C5 saturated azepane **330a** and C4-C5 unsaturated azepane **331a** were formed in 9% and 21% yield, respectively (Scheme 68B). The significant solvent effect on the success of the reaction highlights the difficulty in identifying new reactions of this type.



Scheme 68

2.2.3 (6+1) Carbonylative cyclisation of cyclopropylmethylamides to form azepanes

The (6+1) carbonylative cyclisation of cyclopropylmethylamide **328a** to form azepanes **330a** and **331a** serves as the second example of an intramolecular protocol for the nucleophilic trapping of rhodacyclopentanones discovered in Bristol. Azepanes are prominent heterocycles found in many natural products, which have been the focus of significant interest for both their biological profiles and their synthetically challenging structures.[168] Representative examples of bioactive azepane-based molecules include, the insecticide, (-)-stemaphylline; the potent protein kinase C inhibitor, balanol; and the antibiotic, Mecillinam (Figure 2).[169-171]

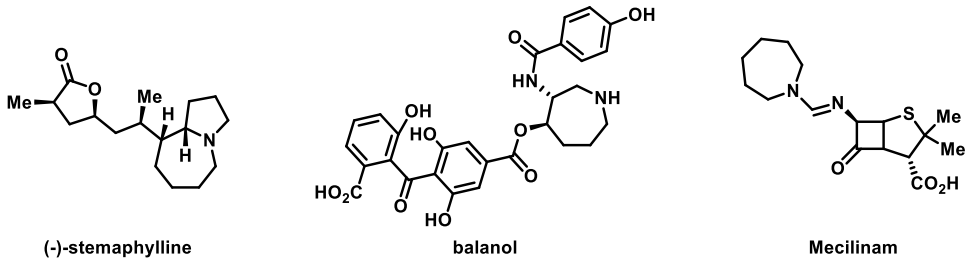
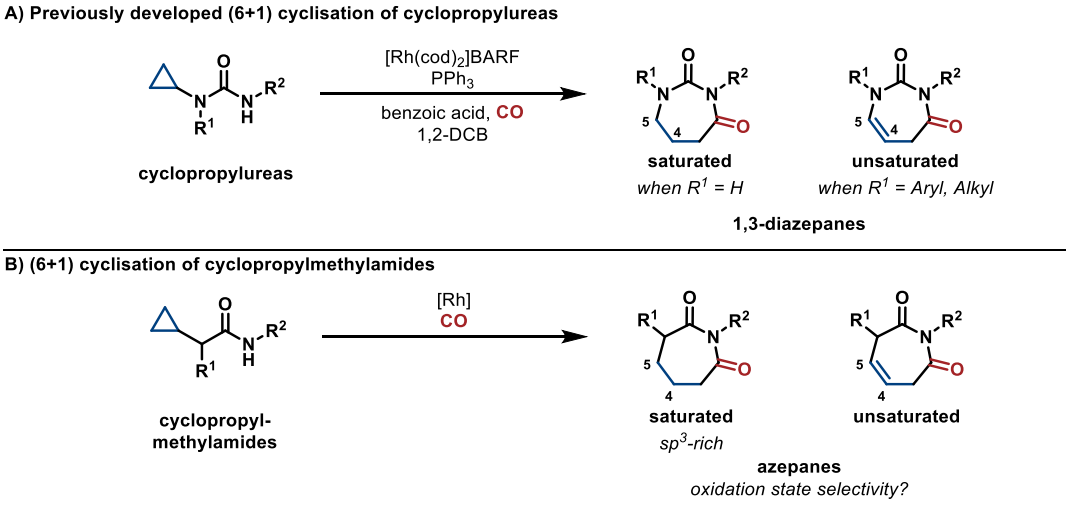


Figure 2: Representative biologically active azepanes.

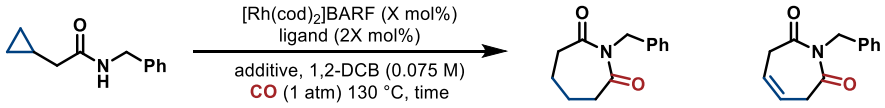
2.2.3.1 Optimisation of the (6+1) carbonylative cyclisation of cyclopropylmethylamides

In Chapter 2, it was shown that the oxidation level of the C4-C5 position of 1,3-diazepanes could be controlled by appropriate substitution of the R^1-position of the cyclopropylurea substrates: when R^1 = alkyl or aryl the unsaturated product is preferred, whereas when R^1 = H the saturated product was preferred (Scheme 69A). A mechanistic explanation for this phenomenon was proposed in Section 2.1.4.1. The subsequently discovered (6+1) carbonylative cyclisation of cyclopropylmethylamides also provided C4-C5 saturated and unsaturated products, control over which would be highly desirable (Scheme 69B). Therefore, optimisation studies were carried out with the aim of improving the overall yield and oxidation level selectivity (for saturated or unsaturated) of the process.



Scheme 69

Selected results from the optimisation of the (6+1) carbonylative cyclisation of cyclopropylmethylamide **328a** are shown in Table 9. Initially, an extensive ligand screen was carried out. An electronically diverse selection of triarylphosphines and triarylarsines was tested, which provided some interesting observations. For example, As(3,5-$(CF_3)_2C_6H_3)_3$, provided a 50% combined yield of azepane products whilst improving the selectivity towards saturated azepane **330a** (1:1.3 **330a**:**331a**) (Entry 2). Interestingly, when the reaction was run in the absence of an additional ligand, saturated azepane **330a** was formed preferentially, albeit with low selectivity (42%, 1.8:1, **330a**:**331a**) (Entry 3). Subsequent attempts to improve the reaction in the absence of an additional ligand failed. Nevertheless, this result suggested that a weakly binding ligand may be suitable. Further screening identified sulfides as interesting ligands, especially di-*n*-propylsulfide which provided a 42% yield with improved selectivity for saturated azepane **330a** (2.1:1, **330a**:**331a**) (Entry 4). Ultimately, the highly electron-deficient triarylphosphine, $P(C_6F_5)_3$, was identified as the optimal ligand, which provided a 72% yield with slightly improved selectivity for the saturated product **330a** (2.4:1, **330a**:**331a**) compared to sulfide ligands (Entry 5).



328a **330a** *saturated* **331a** *unsaturated*

Entry	X	ligand	additive	time	Yield[a] (330a:331a)	328a
1	7.5	PPh_3	-	24 h	30% (1:2.3)	3%
2	7.5	As(3,5-$(CF_3)_2C_6H_3)_3$	-	24 h	50% (1:1.3)	28%
3	7.5[b]	-	-	24 h	42% (1.8:1)	51%
4	7.5	S(*n*-Pr)$_2$	-	46 h	47% (2.1:1)	45%
5	7.5	$P(C_6F_5)_3$	-	24 h	72% (2.4:1)	16%
6	7.5	$P(C_6F_5)_3$	pyridine (5 mol%)	24 h	84% (3.2:1)	7%
7	**5**	$P(C_6F_5)_3$	**pyridine (5 mol%)**	**46h**	**95%[c] (5.3:1)**	**1%**

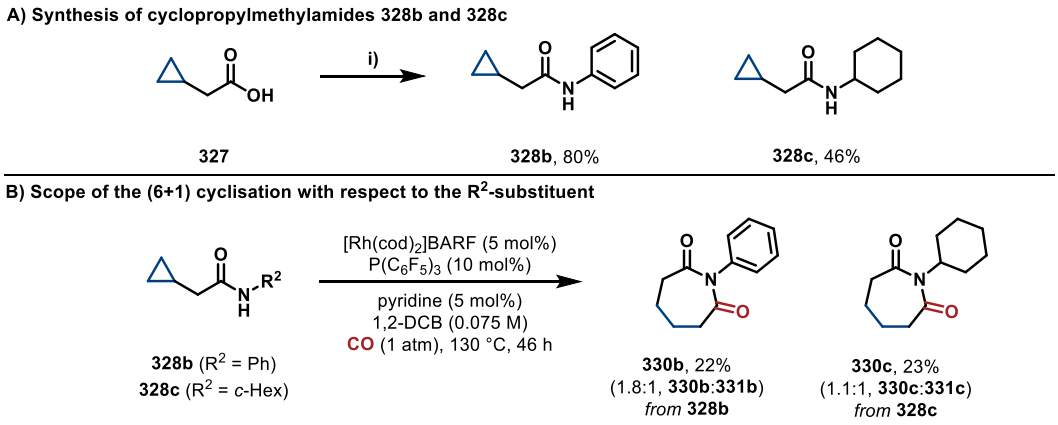
[a]*In-situ* yield measured against an internal standard; [b][Rh(cod)2]BF4 employed as catalyst; [c]Isolated yield.

Table 9: Selected results from the optimisation of the (6+1) carbonylative cyclisation of cyclopropylmethylamide **328a**.

Next, various additives were screened because these have previously been shown to improve the efficiency of related transformations (see Table 1).[102-103] Carboxylic acids and amides did not provide an improvement, but the inclusion of 5 mol% of pyridine improved both the yield (84%) and selectivity (3.2:1, **330a**:**331a**) of the process in favour of the saturated product **330a** (Entry 6). This result is unexpected because basic additives were previously found to inhibit C-C oxidative addition (Section 2.2.2.2). Next, a range of electron-rich and electron-deficient pyridine derivatives (e.g. lutidine), and related heterocycles (e.g. *N*-methylimidazole, quinoline and bipyridine) were screened as additives, but pyridine proved to be optimal. Further optimisation of the reaction parameters provided

the desired product **330a** in an excellent 95% combined yield and 5.3:1 ratio with unsaturated azepane **331a** (Entry 7). Encouragingly, the selectivity for the more sp^3-rich saturated product **330a** increased with the overall efficiency of the process. This is ideal in terms of the overarching aims of this project, which is to develop methodologies for the synthesis of chiral, sp^3-rich heterocycles. It is not clear what the role of pyridine is in this reaction, but pyridine-ligated rhodium-complexes are well known and are catalytically active in several different reactions.[172]

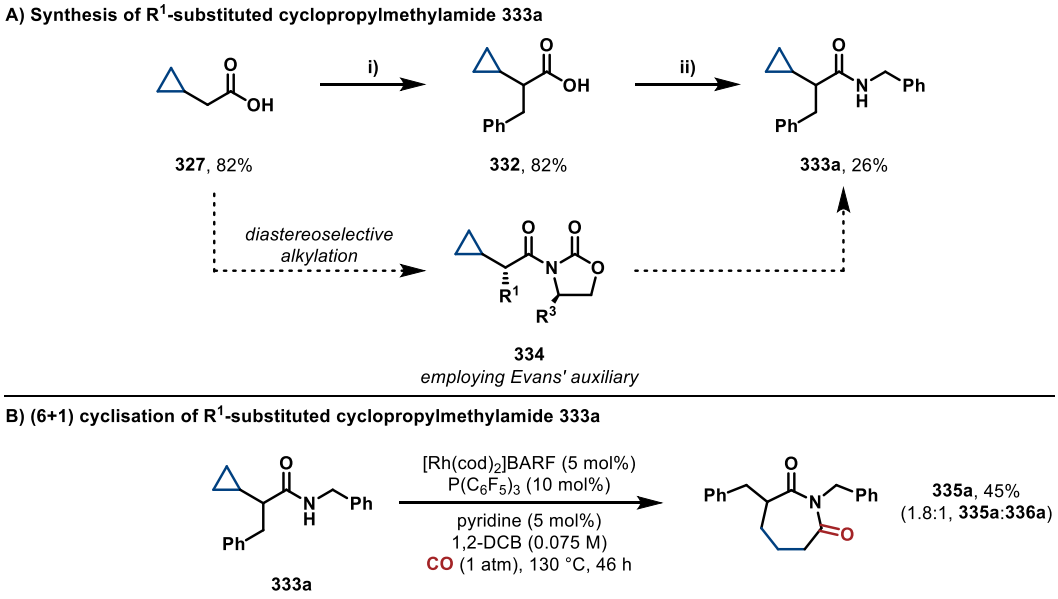
The optimised carbonylative cyclisation conditions were used to investigate the scope of the reaction with respect to the R^1 and R^2 substituents (see Scheme 69). Initially, cyclopropylmethylamides **328b** (R^2 = Ph) and **328c** (R^2 = *c*-Hex) were synthesised because the analogous cyclopropylureas were challenging substrates in the (6+1) carbonylative cyclisation (see Table 4) (Scheme 70A). Both substrates could be formed by EDCI-coupling of carboxylic acid **327** with either aniline (80% yield for **328b**) or cyclohexylamine (46% yield for **328c**), respectively. Under the optimised carbonylative cyclisation conditions, cyclopropylmethylamide **328b** reacted to form desired azepane **330b** in 22% combined yield with poor oxidation level selectivity (1.8:1, **330b**:**331b**) (Scheme 70B). Similarly, cyclohexyl substrate **328c** reacted to form the desired product **330c** in 23% combined yield with essentially no oxidation level preference (1.1:1, **330c**:**331c**).



Scheme 70: A) *Reagents and conditions*: i) EDCI, DMAP, amine, CH_2Cl_2, 0 °C to r.t., 24 h.

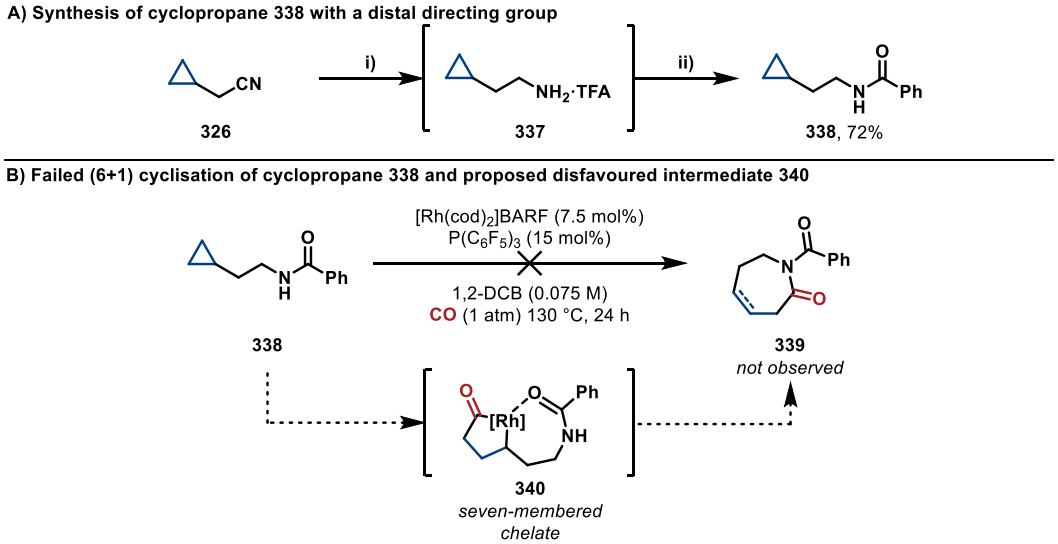
R^1-Substituted cyclopropylmethylamide **333a** was also prepared to investigate the effect of including an R^1 substituent on the cyclisation (Scheme 71A). Carboxylic acid **327** was doubly deprotonated by the addition of two equivalents of LDA before the addition of one equivalent of benzyl chloride, which formed benzyl carboxylic acid **332** in 82% yield. DCC-coupling of carboxylic acid **332** and benzylamine provided R^1-substituted substrate **333a** in 26% yield. It is useful to note that the success of the (6+1) carbonylative cyclisation of cyclopropylmethylamides relies upon the ability to synthesise enantioenriched cyclopropylmethylamides, cyclisation of which would provide access to enantioenriched azepanes. Steps towards this goal might be partially achieved by diastereoselective alkylation of a substrate containing Evans' auxiliary (see alkylation product **334**). This strategy has

been successfully implemented in the asymmetric synthesis of SPPL2a inhibitors.[173] Several alternative methods for the enantioselective alkylation of esters or carboxylic acids exist.[174] When R^1-substituted substrate **333a** was subjected to the carbonylative cyclisation conditions, the desired azepane **335a** was formed in 45% yield with poor oxidation level selectivity (1.8:1, **335a**:**336a**) (Scheme 71B).



Scheme 71: A) *Reagents and conditions*: i) LDA, THF, 0 °C, 15 min *then* benzyl chloride, 35 °C, 3 h; ii) DCC, DMAP, benzylamine, CH_2Cl_2, 0 °C to r.t., 3 h.

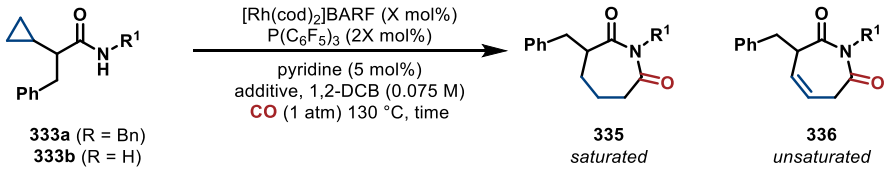
Amide **338** was also investigated whereby the carbonyl of the amide directing group was placed on the other side of the nucleophile relative to the cyclopropane such that carbonylative cyclisation would form azepane **339** (Scheme 72A). The synthesis of **338** was achieved by reduction of nitrile **326** to the amine with *in-situ* generated AlH_3, which was isolated as TFA salt **337**. This was then reacted



Scheme 72: A) *Reagents and conditions*: i) $LiAlH_4$, conc. H_2SO_4, 0 °C to r.t., 15 min *then* **326**, THF, r.t. to 40 °C, 2 h *then* aq. KOH, Et_2O, r.t., 15 min *then* TFA; ii) benzoyl chloride, aq. NaOH, r.t., 10 min.

with benzoyl chloride, under Schotten-Baumann conditions, to form substrate **338** in 72% yield over two steps. When amide **338** was reacted under carbonylative conditions, desired azepane **339** was not observed (Scheme 72B). The failure to cyclise may be due to the requirement of a seven-membered chelate between the directing group and cyclopropane in order to access rhodacyclopentanone **340**.

The previously optimised conditions for parent cyclopropylmethylamide **328a** provided azepane **330a** in excellent yield and moderate selectivity, but the optimised conditions were not applicable to more challenging substrates (i.e. **328b/c** and **333a**). Therefore, a second round of optimisation was carried out on R^1-substituted substrate **333a**, the results of which are summarised in Table 10. Efforts began by reinvestigating the pyridine and ligand loadings, temperature, and duration of the reaction, but no improvement was afforded. Next, the effect of the Rh(I)-catalyst counter-anion was probed. This was achieved by employing neutral Rh(I)-precatalyst, $[Rh(cod)Cl]_2$, and various silver(I) salts (e.g. AgOAc, AgTFA, $AgPF_6$), which form a cationic Rh(I)-catalyst *in-situ*. Encouragingly, when $[Rh(cod)Cl]_2$ and $AgSbF_6$ were employed, azepane **335a** was formed in 45% yield with a slightly decreased selectivity (1.3:1, **335a**:**336a**) for the saturated product (Entry 2). The fact that a comparable yield was achieved by the addition of a silver salt prompted further studies. As a result, it was discovered that the addition of a substoichiometric quantity of AgOAc to a cationic $[Rh(cod)_2]$BARF system improved the yield of saturated azepane **335a** (51%, 1:1.8, **335a**:**336a**) (Entry 3). Ag(I)-additives have previously been utilised in Rh-catalysed C-H activation[175] and C-C activation[176] processes where the role of the silver salt is to either mediate a concerted-metallation-deprotonation step[177-179], or to generate a Ag(I)-nucleophile in a cross-coupling reaction. It is unclear what the role of the silver salt is in the current process.



333a (R = Bn)
333b (R = H)

335
saturated

336
unsaturated

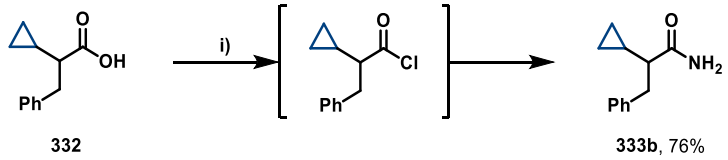
Entry	R^1	X	additive	time	Yield[a] (335:336)
1	Bn	5	-	24 h	45% (1.8:1)
2	Bn	3.75[b]	$AgSbF_6$ (7.5 mol%)	24 h	45% (1.3:1)
3	Bn	7.5	AgOAc (7.5 mol%)	24 h	51% (1:1.8)
4	H	7.5	$AgCO_3$ (15 mol%)	24 h	74% (1.7:1)
5	**H**	**5**	**$AgCO_3$ (10 mol%)**	**46 h**	**79% (2.0:1)**

[a]*In-situ* NMR yield measured against an internal standard; [b]$[Rh(cod)Cl]_2$ employed as catalyst; [c]Isolated yield.

Table 10: Selected results from the optimisation of the (6+1) carbonylative cyclisation of R^1-substituted substrates **333**.

Having thoroughly investigated each parameter of the catalytic system, the R^2-substituent was optimised. Primary amide **333b** was synthesised in 76% yield from carboxylic acid **332** *via* reaction of

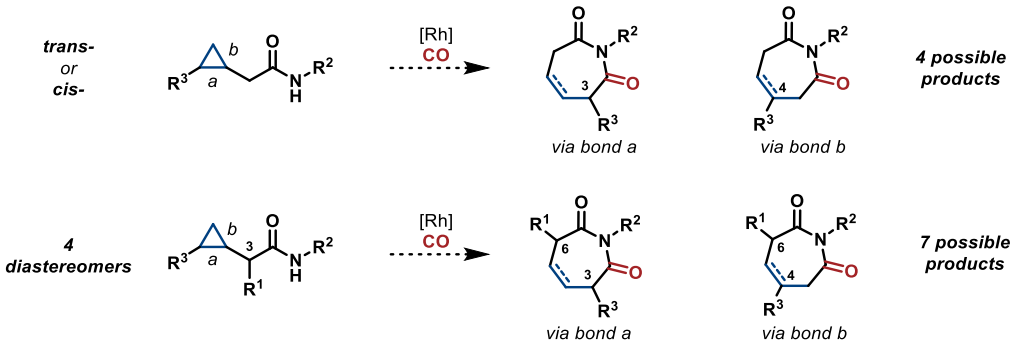
the corresponding acid chloride with aqueous ammonia (Scheme 73). Fortunately, primary amide **333b** cyclised with good efficiency to form azepane **335b** in 74% combined yield and a 1.7:1 ratio with unsaturated analogue **336b** (Entry 4, Table 10). Further modification of the reaction parameters increased the yield to 79% over two days, but failed to improve C4-C5 oxidation level selectivity (2:1 **335b**:**336b**) (Entry 5).



Scheme 73: Synthesis of primary cyclopropylmethylamide **333b**. A) *Reagents and conditions*: i) $(COCl)_2$, cat. DMF, CH_2Cl_2, 0 °C, 30 min *then* aq. NH_3, r.t., 30 min.

2.2.3.2 Cyclopropylmethylamides containing 1,2-disubstituted cyclopropanes

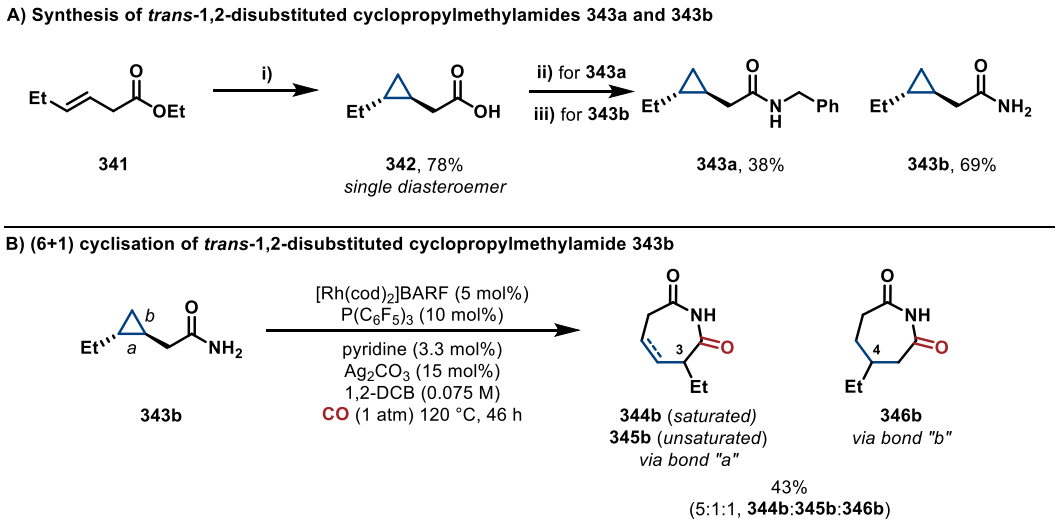
Expansion of the scope of the (6+1) carbonylative cyclisation of cyclopropylmethylamides to include 1,2-disubstituted cyclopropanes (substitution at R^3) would be a valuable addition to this methodology because it would allow access to many diversely functionalised (and enantioenriched) azepanes (Scheme 74). However, the diastereoselective and enantioselective synthesis of R^1- and R^3-substituted cyclopropylmethylamide substrates appeared to be challenging. Furthermore, carbonylative cyclisation of R^3-substituted cyclopropylmethylamides could give rise to four possible azepanes (C3 vs C4 substituted, saturated vs unsaturated) and R^1,R^3-disubstituted cyclopropylmethylamides could give rise to seven possible azepanes. Therefore, the (6+1) carbonylative cyclisation must be highly regio- and oxidation level selective in order to be synthetically useful.



Scheme 74: Stereochemical considerations arising from the (6+1) carbonylative cyclisation of cyclopropylmethylamides containing 1,2-disubstituted cyclopropanes.

Preliminary studies into the application of 1,2-disubstituted cyclopropylmethylamides to the (6+1) carbonylative cyclisation began with the synthesis of *trans*-cyclopropanes **343a** and **343b** (Scheme 75A). The synthesis was achieved starting from commercially available β,γ-unsaturated ester **341**, which underwent a Simmons-Smith cyclopropanation and ester hydrolysis to form carboxylic acid

342 in 78% yield, as a single diastereomer. Secondary amide **343a** was formed in 38% yield from carboxylic acid **342** by EDCI-coupling with benzylamine. Primary amide **343b** was formed in 69% yield by converting carboxylic acid **342** to the corresponding acid chloride and reacting it with aqueous ammonia. Under the optimised (6+1) carbonylative cyclisation conditions, secondary amide **343a** provided an intractable mixture of products. However, when primary amide **343b** was reacted under carbonylative cyclisation conditions, C3-substituted azepane **344b** formed preferentially, but as a mixture consisting of both saturated and unsaturated variants of the C4-regioisomer (5:1:1, **344b**:**345b**:**346b**) in 43% combined yield (Scheme 75B). The disappointing selectivity observed in this reaction mimics that observed for *trans*-1,2-disubstituted cyclopropylureas (Section 2.1.3.2, Table 7).

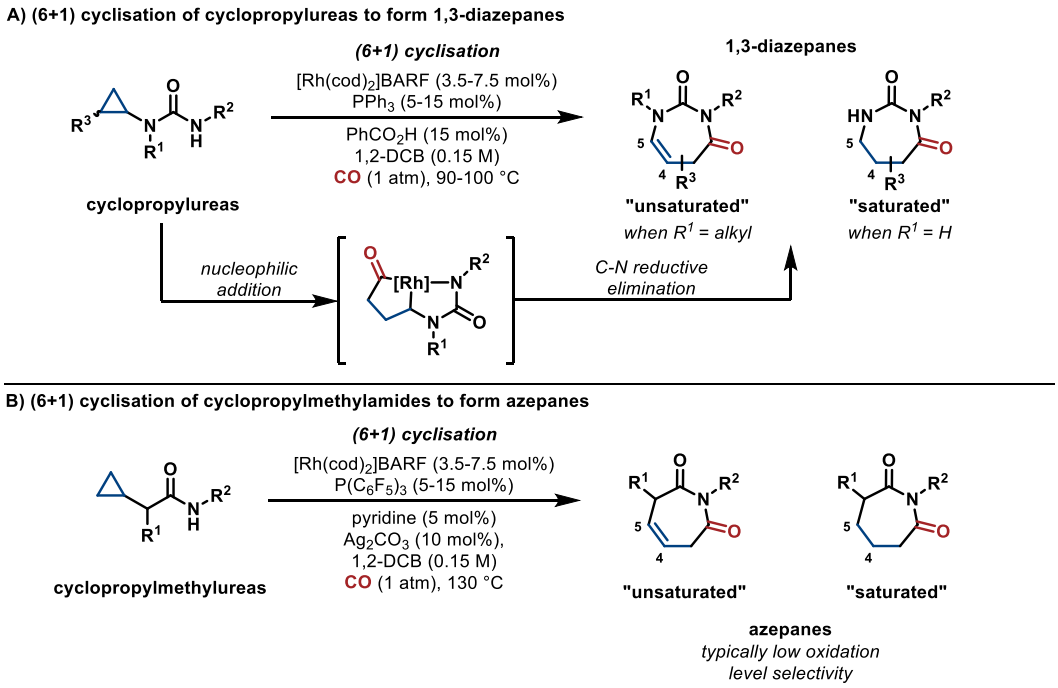


Scheme 75: A) *Reagents and conditions*: i) CH_2I_2, Et_2Zn, CH_2Cl_2, -10 °C to r.t., 2 h *then* aq. NaOH, reflux, 1 h; ii) EDCI, DMAP, benzylamine, CH_2Cl_2, 0 °C to r.t., 24 h; iii) $(COCl)_2$, cat. DMF, CH_2Cl_2, 0 °C, 30 min *then* aq. NH_3, r.t., 30 min.

2.3 Summary and conclusions from the studies in Chapter 2

Building on the discovery made by McCreanor, a protocol for (6+1) carbonylative cyclisation of cyclopropylureas to form 1,3-diazepanes by intramolecular nucleophilic addition of *N*-nucleophiles to rhodacyclopentanones has been developed (Scheme 76A). It was found that the oxidation level of the C4-C5 position of the diazepanes could be controlled by appropriate choice of the cyclopropylurea R^1-substituent, specifically: when R^1 = alkyl or aryl the unsaturated diazepane forms preferentially, but when R^1 = H the saturated diazepane forms preferentially. Mechanistic studies suggest that this is due to reversible β-hydride elimination. The scope of the (6+1) carbonylative cyclisation was found to include various alkyl and aryl group at R^1 and R^2, with the exception of R^2-aryl trisubstituted cyclopropylureas. Additionally, cyclopropylureas containing 1,2-disubstituted cyclopropanes were investigated, which were found to react *via* Rh(I)-addition to the unexpected cyclopropyl C-C bond,

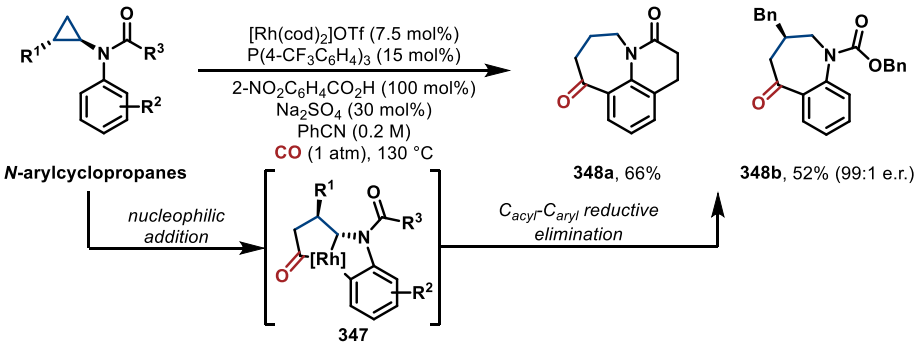
based on previous studies carried out at Bristol. A rationale for this observation was proposed based on reversible rhodacyclopentanone formation.



Scheme 76

The (6+1) carbonylative cyclisation of cyclopropylureas served as a proof of concept for a general strategy for the formation of medium-sized rings by intramolecular nucleophilic addition to rhodacyclopentanones. Investigations into the generality of this strategy were carried out, which led to the discovery of a second protocol for the (6+1) carbonylative cyclisation of cyclopropylmethylamides to give azepanes (Scheme 76B). Optimisation studies identified pyridine and Ag(I)-salts as beneficial additives in this process. At the present level of development, azepanes bearing R^1- and R^2-primary alkyl substituents are formed in high yield, but with poor selectivity over the oxidation level of the C4-C5 position. Further optimisation of the oxidation level selectivity of the process is required.

Subsequent research carried out at Bristol has identified several other methodologies based on intramolecular nucleophilic addition to rhodacyclopentanones. For example, Wang and co-workers discovered that rhodacyclopentanones **347**, generated from *N*-arylcyclopropanes, could promote C-H metallation of the adjacent aryl (or vinyl) group en route to benzazepanes (e.g. **348a** and **348b**) (Scheme 77).[105] Several other related processes are currently in development at Bristol.



Scheme 77: Wang's protocol for the synthesis of benzazepanes from *N*-arylcyclopropanes.

Future directions in this project should focus on identifying the role of the various additives (amides/carboxylic acids, pyridine, Ag(I)-salts), and gaining a better understanding of the factors governing successful nucleophilic addition to rhodacyclopentanones. Progress towards either of these goals might benefit the development and expansion of related processes.

Chapter 3 – Studies towards the total synthesis of otonecine and related pyrrolizidine alkaloids

3.1 Introduction

In Chapter 2, the discovery and development of methodologies that employ nucleophilic addition to rhodacyclopentanones as the key mechanistic step was presented. Chapter 3 describes the application of a rhodacyclopentanone-based methodology, developed at Bristol, to the total synthesis of the natural product otonecine and related pyrrolizidine alkaloids. Section 3.1 will introduce the pyrrolizidine alkaloids and the natural product otonecine. An emphasis will be placed on the unique structure of otonecine and a transannular interaction, which is characteristic of this ring system. Previous total syntheses of (*rac*)-otonecine, and related studies, will then be discussed before the goals of this project are set out. In Section 3.2, studies carried out at Bristol towards the total synthesis of otonecine are presented. The later portions of Chapter 3 regard studies towards the synthesis of the necic acids of the otonecine-type pyrrolizidine alkaloids. Section 3.3.1 introduces previous synthesise of the necic acids and Section 3.3.3 covers research carried out at Bristol towards the development of a short enantioselective synthesis of these components.

3.1.1 The pyrrolizidine alkaloids

The pyrrolizidine alkaloids (PAs) are a large family of over 660 natural compounds found in approximately 6000 species of flowering plant, where they are produced as a defence against grazing animals.[180-181] The widespread occurrence of toxic PAs is problematic for livestock and humans who might accidentally ingest PAs through the consumption of PA containing plants or contaminated animal produce.[182-184] In extreme cases, PA poisoning has been known to kill both livestock and humans.

3.1.1.1 Structure of the pyrrolizidine alkaloids

The pyrrolizidine alkaloids are defined by the presence of a functionalised pyrrolizidine ring (indicated in blue), known as a necic base, which is typically substituted with combinations of hydroxyl and hydroxymethyl groups (Figure 3A).[185] Approximately half of the necic bases are unsaturated at the C1-C2 position, which is a necessary structural feature for the biological activity of this family of natural compounds.[186] Additionally, most necic bases also occur as the *N*-oxide. Variations of these structural features gives rise to many diverse and stereochemically-rich necic bases as demonstrated in Figure 3A.[187] The five most common necic bases are structurally related to retronecine as they each contain C1-hydroxymethyl and C7-hydroxyl substituents (Figure 3B). For example, heliotridine is the C7-epimer of retronecine and platynecine is the C1-C2 saturated version. Otonecine is unique among the

necic bases because it is an eight-membered ring, which lacks the ring junction N-C8 bond of the pyrrolizidine ring system. The ring junction bond is replaced with a *N*-methyl substituent and C8-ketone.

Typically, the necic bases are attached *via* ester linkages to one or more necic acids.[185, 187] The structures shown in Figure 3C are representative of the types of ester linkages formed between necic acids and bases. Monoesters, such as lycopsamine, contain a single ester linkage, and diesters, such as 7,9-diangeloylplatynecine, contain two necic acids joined by two ester linkages. The most common type of ester linkage, and most important in terms of the research contained in this chapter, is that which form macrocyclic diesters, such as senecionine. Here, the necic base is bound to a single dicarboxylic necic acid through two ester linkages at the C7 and C9 positions, resulting in the formation of a macrocycle.

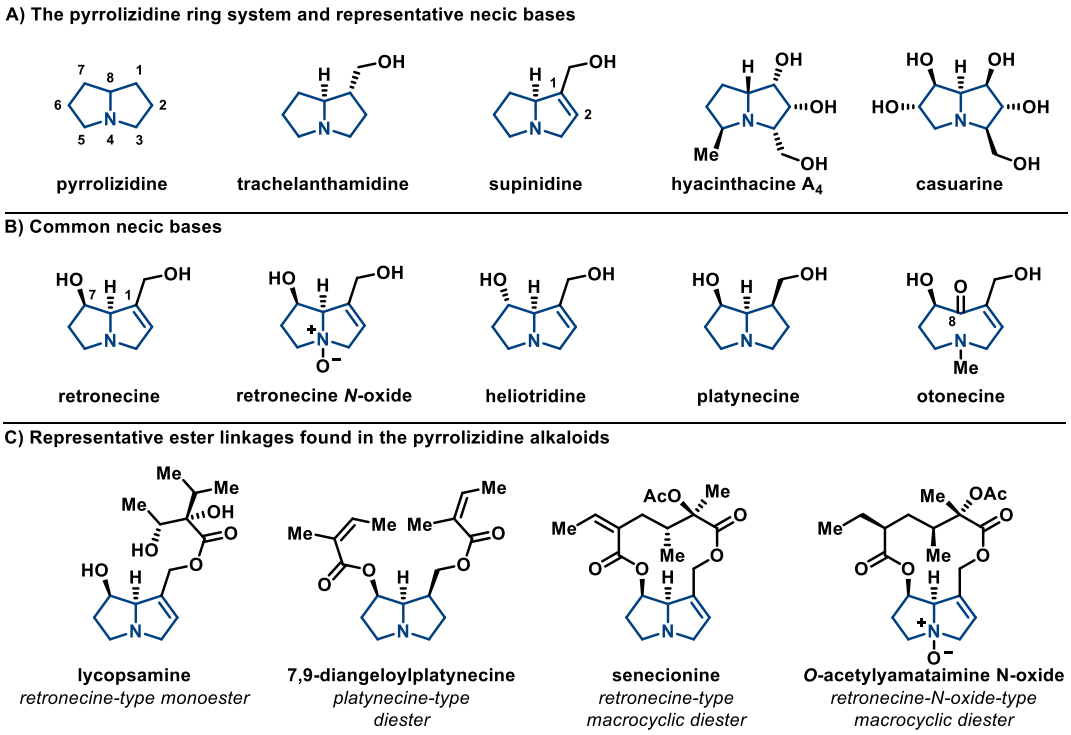


Figure 3

The pyrrolizidine alkaloids are categorised by the type of ester linkages, and the largest category is the senecionine-type PAs, which are macrocyclic diesters composed of the necic bases shown in Figure 3B and a C_{10} dicarboxylic necic acid.[188] A generic structure of a senecionine-type PA is shown in Figure 4A. Here, the necic base is bound *via* ester linkages at the C7 and C9-positions to the C16 and C11-position of the necic acid, respectively, resulting in a 12-membered macrocycle. Integerrinecic acid is representative of the most basic and common C_{10} dicarboxylic acids, important structural features of which are the C12,C13-vicinal stereocentres and the C15-exocyclic alkene (Figure 4B). All four diastereomers resulting from epimerisation of the C12-stereocentre and isomerisation of the C15-

exocyclic alkene are known, and each of these has been isolated as part of an otonecine-type macrocyclic diester (Figure 4C). In addition, many otonecine-type macrocyclic diesters are known that contain higher functionalised necic acids, such as those shown in Figure 4D.

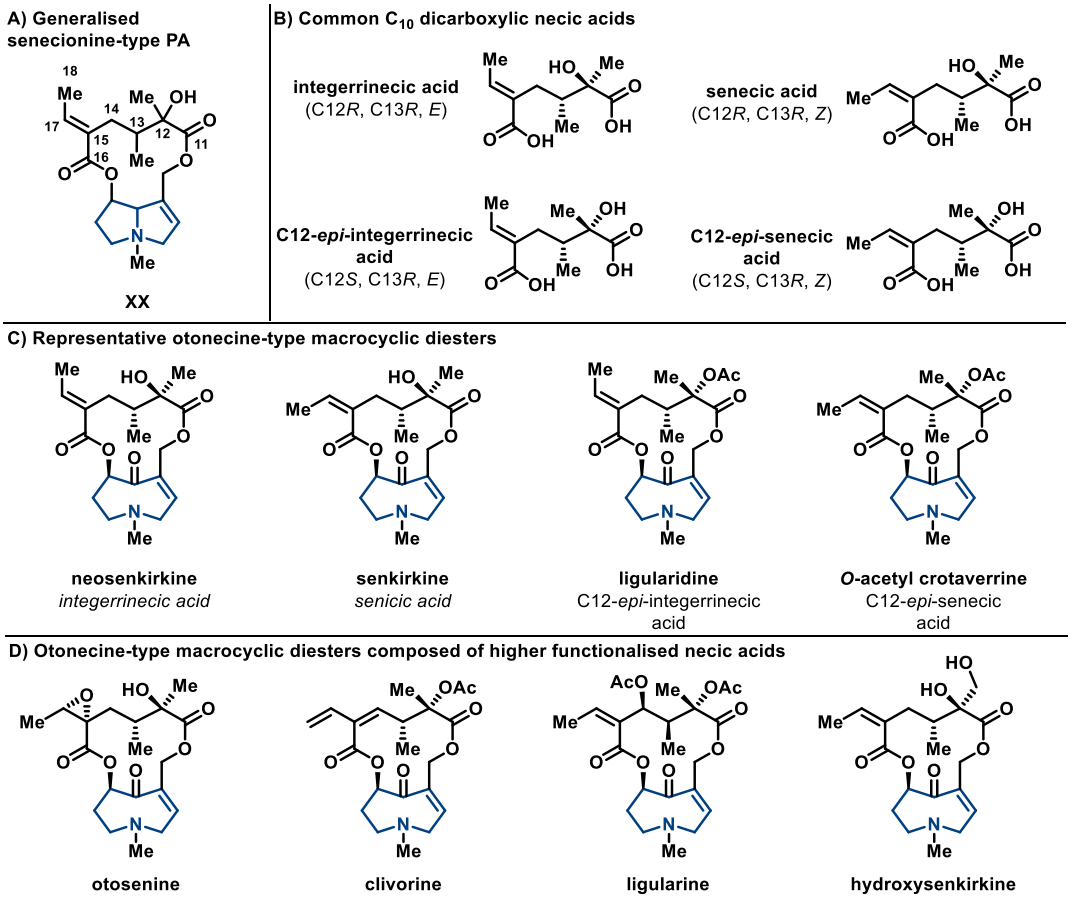


Figure 4

3.1.1.2 Otonecine

Otonecine was first isolated in 1941 by Zhdanovich and Menshikov[189], but it took a further 26 years before Koretskaya and co-workers determined its exact structure.[190-191] The first two crystal structures of otonecine-type PAs revealed a unique structural feature of the otonecine ring system. The first, disclosed by Wunderlich in 1967, was a CSA salt of retusamine in which the C8-ketone existed as a hemiaminal because of a transannular covalent bond between the tertiary amine and C8-position of the necic base (Figure 5A).[191] The second crystal structure, published by Birnbaum in 1972, was of a free base of clivorine (Figure 5B).[192] This also revealed a significant transannular interaction between the tertiary nitrogen and C8-carbon centre (N-C8 distance 1.99 Å), although this was weaker due to the absence of CSA. It is noteworthy that the transannular interaction causes the otonecine ring system to adopt a boat-boat conformation, which is similar to the pyrrolizidine ring of related PAs, and is vital for the biological mode of action of these compounds. Further evidence for the transannular interaction was measured by Furuya and Asada, who reported the ketone stretching frequency of ligularidine (see

Figure 4, C) to be 1610 cm^{-1},[193] which is significantly weaker than is expected for linear ketones (1725–1705 cm^{-1})[194] or α,β-unsaturated ketones (1685–1665 cm^{-1}).[194]

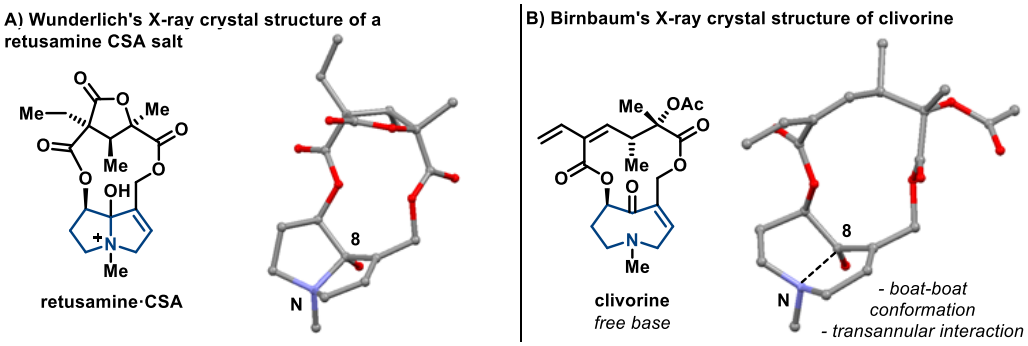
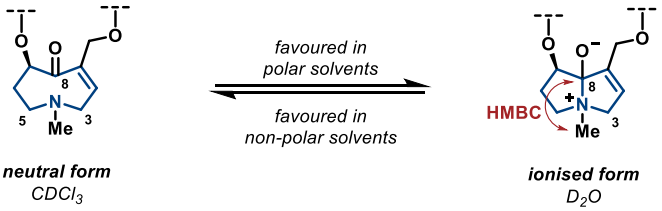


Figure 5

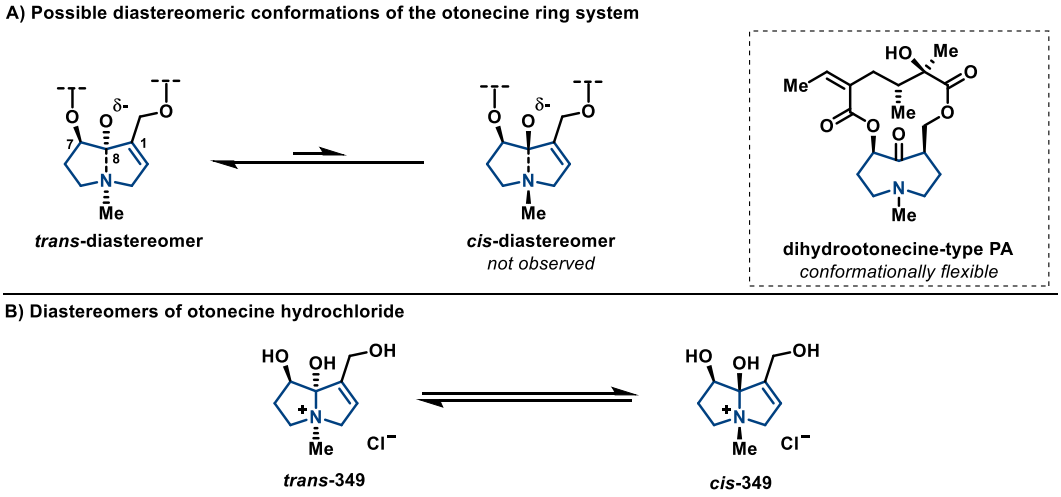
The defining structural characteristic of otonecine is the transannular interaction between the tertiary amine lone pair and the σ*-orbital of the C8-ketone. This interaction defines the conformation, reactivity and biology of the free necic base and that of the otonecine-type macrocyclic diesters, and so has been researched extensively. The transannular interaction bestows otonecine-type PAs with unusual properties, which distinguish them from other PAs. Perhaps most significant is a dual-solubility in both non-polar and polar solvents, including water.[195-196] This property was investigated by Lin and co-workers, who compared the ^{1}H and ^{13}C NMR spectra of the otonecine-type PA, clivorine, when dissolved in *d*-chloroform and deuterium oxide (Table 11).[197] The investigation revealed that otonecine exists in its neutral form when dissolved in *d*-chloroform (non-polar solvent) as determined by the ^{13}C-chemical shift of C8 (δ_C 192.2 ppm). However, when characterised in deuterium oxide (polar solvent), the chemical shift of the C8-position underwent a significant upfield shift (δ_C 145.1 ppm) indicating that the azocane adopts an ionised form where the transannular interaction was maximised (i.e. a N-C8 covalent bond was present). Additionally, significant downfield shifts were measured for C3 and C5, and an HMBC correlation between the *N*-methyl protons and C8 was present in deuterium oxide. Such dual-solubility makes otonecine-type PAs highly bioavailable.



Position	δ_H (ppm)	δ_C (ppm)	Position	δ_H (ppm)	δ_C (ppm)
3	3.35	58.8	3	3.82	66.7
	3.17	-		3.69	-
5	2.90-2.84	53.3	5	3.39	60.8
	2.70	-		3.21	-
8	-	192.2	8	-	145.1

Table 11: Selected ^{1}H and ^{13}C chemical shifts of the otonecine-ring system of clivorine in non-ionised and ionised forms.

Another consequence of the strong transannular interaction is the otonecine ring system can adopt two "diastereomeric" conformations where the *N*-centre and C8-centre might be considered stereocentres.[198] This effect is illustrated by the *trans*-diastereomer and *cis*-diastereomer, shown in Scheme 78A, where the *N*-methyl and C8-oxygen substituents are positioned either *trans* or *cis* to the C7-alcohol. Evidence gained through NMR and crystallographic studies showed that otonecine-type macrocyclic diesters exist solely as the *trans*-diastereomer, which is believed to be a result of the rigidifying influence of the macrocycle.[199] However, Röder and Liu reported that a macrocyclic diester of *dihydro*otonecine (see the dashed box) existed as an equilibrating mixture of the *trans*- and *cis*-diastereomers, which implies that the C1 alkene of otonecine is also a stabilising feature.[200]



Scheme 78

In the absence of a rigidifying macrocycle, otonecine can interconvert between both diastereomeric forms. Röder carried out an in-depth NMR analysis of otonecine hydrochloride, which

was found to exist as an equilibrium mixture of diastereomeric bicyclic salts ***trans*-349** and ***cis*-349** (δ_C(8) 119.0 ppm and 120.1 ppm, respectively) (Scheme 78B). No detailed NMR analysis of the free base of otonecine has been carried out, but empirical observations indicate that the transannular interaction is reasonably weak and that the ring is conformationally flexible. For example, otonecine can form an oxime, which indicates that C8 is ketonic in reactivity.[198] Additionally, otonecine has proved recalcitrant to crystallisation, and its NMR spectra are broad at room temperature.[201]

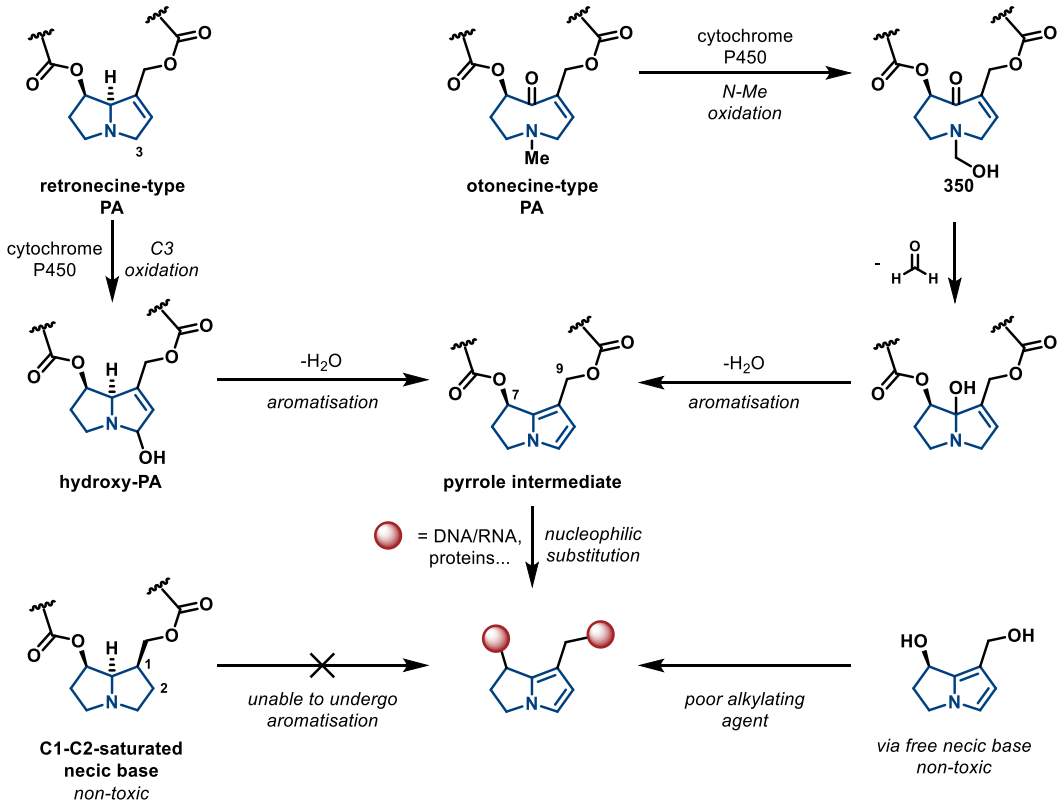
Interestingly, study of the various crystal structures of otonecine-type PAs allowed Bürgi and Dunitz to deduce the ideal angle of attack of a nucleophile onto a carbonyl.[202] The authors measured N-C8 bond distances of the crystal structures of several otonecine-type PAs and methadone (which exhibits a similar Nn-C(O)σ* interaction), and found that they ranged from 1.5 Å (i.e. a covalent bond) to 3 Å (i.e. a dipole-dipole interaction). The authors treated each crystal structure as a single reaction coordinate for the addition of a nucleophile to a carbonyl. They reported that as the N-C8 bond distance becomes shorter, the C8-carbonyl becomes less planar and more tetrahedral, suggesting a transition from sp^2 to sp^3 hybridisation. Furthermore, it was found that the nitrogen nucleophile approached the carbonyl in a straight line at a constant angle of 107°, which the authors concluded to be the strongly preferred orientation for nucleophilic attack onto a sp^2-centre. Further evidence for this conclusion was later provided by theoretical calculations.[203]

3.1.1.3 Biological aspects

Many pyrrolizidine alkaloids are hepatotoxic, carcinogenic, genotoxic, teratogenic and occasionally pneumotoxic to humans and animals.[185] Human exposure to PAs typically occurs through the ingestion of contaminated grains, vegetables, salads or animal products such as honey and milk.[204] Developing countries are typically the worst affected by PA poisonings, however, developed countries are becoming increasingly at risk due to increasing consumption of teas and herbal remedies.[205] One particularly catastrophic outbreak of PA poisoning took place in Afghanistan in 1974 to 1975 where contaminated bread was responsible for 7200 cases of liver disease and 1600 deaths.[206-207] As a result of the threat to public health, the European Medicines Agency recommended a maximum daily intake of 0.35 μg PAs/day.[208]

The pyrrolizidine alkaloids themselves are non-toxic, but become metabolically activated in the liver.[209-211] Metabolic activation of bicyclic pyrrolizidines, such as retronecine, is initiated by cytochrome P450-mediated oxidation of the C3-position (Scheme 79). The resulting hydroxy-PA rapidly aromatises upon elimination of the C3-hydroxide to form a pyrrole intermediate. The benzylic C7 and C9 esters of the pyrrole intermediates are activated towards nucleophilic substitution, and can react with nucleophilic amino acid residues, DNA/RNA bases and other nucleophiles, thereby exerting a toxic effect. Additionally, macrocyclic diesters can cross-link DNA giving them a greater toxic potential than monoester PAs.[187] As was mentioned earlier, C1-C2-*saturated* PAs are considered non-toxic because

they are unable to form pyrrole intermediates.[210] Otonecine possesses identical biological activities to retronecine because it converges on the same reactive pyrrole intermediates upon metabolic activation. In this case, cytochrome P450 mediated oxidation of the *N*-methyl substituent forms hemiaminal **350**.[212] Elimination of formaldehyde forms a secondary amine, which undergoes a spontaneous transannular condensation onto the ketone forming pyrrole intermediates. As a result of metabolic activation of PAs taking place in the liver, it is here where most of the damage is caused.[213]



Scheme 79: Formation of a toxic pyrrole intermediate upon metabolic activation of retronecine-type and otonecine-type PAs.

PAs can also be "metabolically deactivated".[187] For example, ester hydrolysis of PAs reduces the alkylating ability of the corresponding pyrrole intermediates. For this reason, free necic bases (such as otonecine) are not as toxic as their esters, but can still be activated under acidic conditions. Additionally, the free necic bases are more water soluble than the esters, which aids their excretion, or transport to other locations in the body.[214-215]

PAs have been investigated as treatments for numerous diseases. Several PAs have shown anti-bacterial activity including the retronecine-type PA, usaramine, which can inhibit the formation of protective biofilms by certain bacteria, although the mechanism for this remains unclear.[216] Another retronecine-type PA, indicine-*N*-oxide, was used to treat children with acute lymphoblastic leukaemia, which provided positive results.[217] Unfortunately, this required very high doses of the active compound

(2000 mg/m^2/day), which resulted in mild hepatotoxicity. PAs have been investigated for several other therapeutic effects including the treatment of inflammation, HIV and Alzheimer's.[185]

3.1.2 Previous total synthesis of otonecine

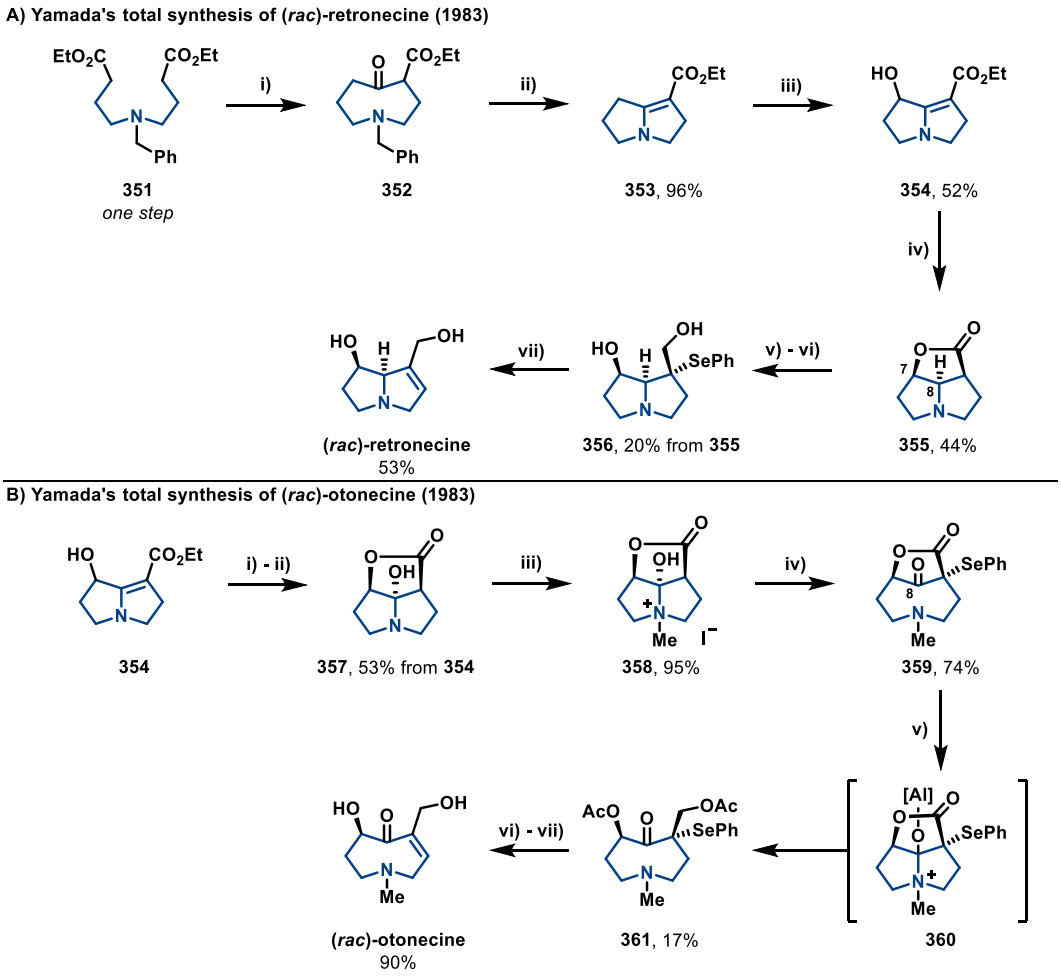
This section concerns previous efforts towards the total synthesis of (rac)-otonecine and related studies. Previous synthesises of the necic acid portions of otonecine-type PAs and methods for forming macrocyclic diesters are summarised later in Section 3.3.1.

The diverse and complex structures of the pyrrolizidine alkaloids in combination with their potent biological activities makes them an appealing target for synthesis. In particular, the small size and high stereochemical density of the necic bases has resulted in them becoming a proving ground for new methodologies. In contrast, otonecine has only been synthesised twice before, both times as a racemate. Consequently, none of the otonecine-type macrocyclic diesters have been synthesised. The lack of synthetic efforts towards the otonecine-type PAs perhaps reflects both the difficulty in synthesising medium-sized rings and the innately challenging otonecine ring system. The many synthetic routes to the Pyrrolizidine Alkaloids have been covered in a series of reviews.[218-236]

The first total synthesis of (*rac*)-otonecine was published by Yamada and co-workers in 1983.[237-238] Described over two papers is a divergent synthesis of both (*rac*)-retronecine and (*rac*)-otonecine *via* common intermediate **354** (Scheme 80A).[239] The synthesis of common intermediate **354** began with Dieckmann cyclisation of diester **351** to form azocane **352**. Benzyl deprotection of azocane **352** caused the resulting secondary amine to undergo a spontaneous transannular condensation onto the ketone to form pyrrolizidine **353**. γ-Oxidation of the α,β-unsaturated ester provided common intermediate **354**. The synthesis of (*rac*)-retronecine was completed by alkene reduction of intermediate **354**, which allowed the isolation of the correct C7,C8-diastereomer as lactone **355**. From here, the C1-C2 alkene was installed by *via* selenide **356** to provide (*rac*)-retronecine in 8 steps overall.

Yamada's divergent synthesis of (*rac*)-otonecine from common intermediate **354** began with a sulfur-Michael addition/oxidation sequence to form lactone **357** (Scheme 80B). *N*-Methylation and treatment with NaH and PhSeCl simultaneously cleaved the ring junction N-C8-bond to reveal the azocane ring and install the selenium functionality of **359**. Yamada then took advantage of the N-C8 transannular interaction to carry out a chemoselective reduction of the lactone, in the presence of reducible ketone and phenylselenide functionalities. The lactone reduction was achieved by treating lactone **359** with diethylaluminium chloride, which promoted the formation of aminal **360** where the ketone is masked. Lactone reduction using DIBAL-H, and acetylation of the resulting diol formed diacetate **361** in 17% yield upon unmasking of the ketone during work-up. The synthesis of (*rac*)-otonecine was completed in 11 total steps by elimination of the phenylselenide moiety of diacetate **361**

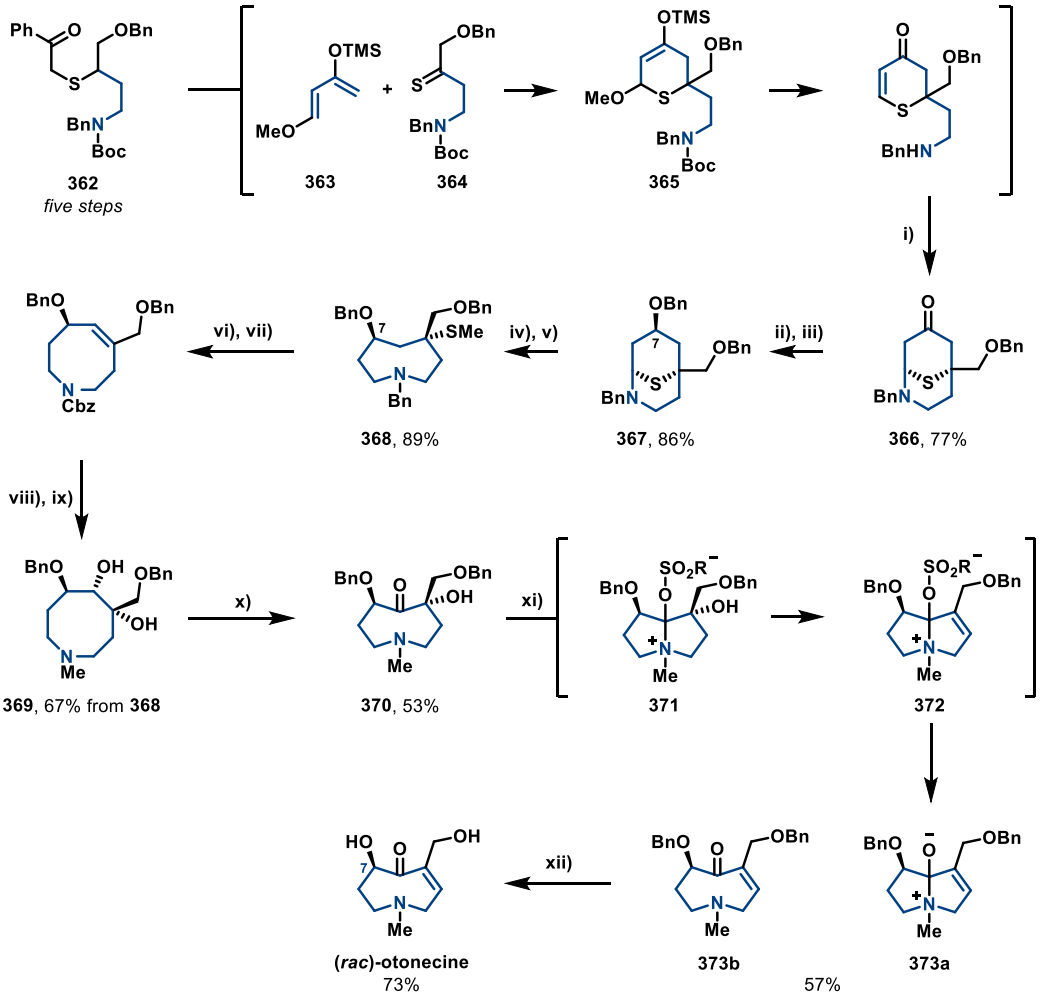
and deacetylation of the alcohols. Yamada's seminal report remains the shortest total synthesis of (*rac*)-otonecine to date.



Scheme 80: A) *Reagents and conditions (some details were not provided by the authors)*: i) KO*t*-Bu, xylene, reflux, 56 h, yield not provided; ii) Pd/C, H_2, EtOH, 40 min, 96%; iii) LDA, THF, -78 °C, 100 min *then* MoO_5·py·HMPA, -78 °C, 20 min, 52%; iv) PtO_2, H_2, MeOH, r.t., 3 h, 44%; v) LDA, Ph_2Se_2, HMPA, THF, -50 °C, 90 min, 21%; vi) $LiAlH_4$, THF, -10 °C, 2 h, 95%; vii) 30% H_2O_2/AcOH, r.t., 1.5 h, 53%. B) *Reagents and conditions*: i) LiSPh, PhSH/THF, r.t., 2 h, 70%; ii) $Hg(OAc)_2$, AcOH/H_2O, r.t. to 90 °C, 1 h, 76%; iii) MeI, acetone, reflux, 1 h, 95%; iv) NaH, PhSeCl, THF, r.t., 40 min, 74%; v) DIBAL, $AlClEt_2$, PhMe, 45 °C, 1 h *then* Ac_2O, pyridine, r.t., 5 h, 17%; vi) 30% H_2O_2, AcOH, r.t., 2 h; vii) NaOMe, MeOH, r.t., 30 min, 90% from **361**.

The second total synthesis of (*rac*)-otonecine, published by Vedejs and co-workers in 1998, utilised a thioketone cycloaddition to form the azocane ring (Scheme 81).[201,240] After significant investigation, thioether **362** (available in 5 steps) was identified as a viable substrate for the key cycloaddition. Upon irradiation with visible light in a highly purified solution of benzene, the thioether moiety of thioether **362** underwent a Norrish type-2 fragmentation to form thioketone **364**, which underwent further cycloaddition with the Danishefsky diene **363**. Resulting adduct **365** was treated with trifluoroacetic acid to reveal both the secondary amine and α,β-unsaturated ketone, which underwent a

spontaneous Michael addition forming bicyclic thioaminal **366** in 77% yield. The protected C7-alcohol of otonecine was installed by reduction of the ketone of thioaminal **366** and benzyl protection.



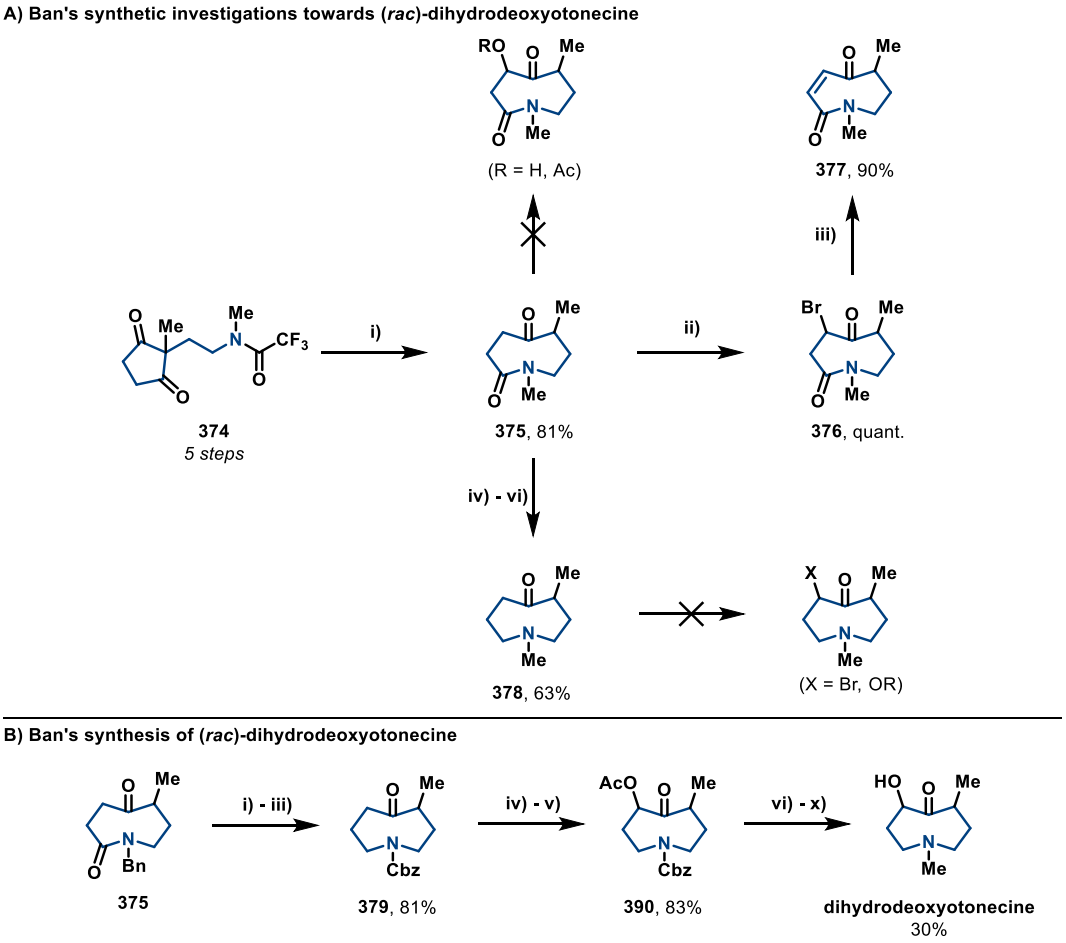
Scheme 81: Vedejs' total synthesis of (*rac*)-otonecine. *Reagents and conditions*: i) hν, PhH, r.t., 12 h *then* trifluoroacetic acid, CH_2Cl_2, r.t., 5 h, 77%; ii) L-Selectride, THF, r.t., 3 h, 97%; iii) NaH, imidazole, BnBr, THF/DMF, 0 °C to r.t., 11 h, 88%; iv) $NaBH_3CN$, AcOH, TFE, r.t., 48 h; v) MeI, DBU, PhH, r.t., 14 h, 89% from **367**; vi) CbzCl, THF, r.t., 16 h, 95%; vii) tetrabutylammonium oxone, CH_2Cl_2, 0 °C, 1.5 h, 89%; viii) $LiAlH_4$, THF, 0 °C to r.t., 8 h, 96%; ix) OsO_4, TMEDA, THF, -70 °C, 42 h, 81%; x) OsO_4, $K_3Fe(CN)_6$, CaO, *t*-BuOH/H_2O, r.t., 55 min, 53%; xi) Burgess reagent, C_6D_6, r.t. to 36 °C to reflux, 36 h, 57%; xii) TMSOTf, thioanisole, CD_3CN, 0 °C, 30 min, 73%.

At this point, the azocane ring was revealed and efforts were directed to installing the C8-ketone and C1-C2 alkene of otonecine. Thioaminal **367** was reduced and *S*-methylated provided azocane **368**, which was transformed into diol **369** over four steps. Oxidation of the secondary alcohol of diol **369** was complicated by transannular nucleophilic attack by the tertiary amine, but was eventually achieved using osmium tetroxide-mediated conditions to form ketone **370**. Ketone **370**, containing both the tertiary amine and ketone of otonecine, existed as a mixture of non-ionised and ionised forms resulting in highly temperature- and pH-dependent NMR spectra. Interestingly, treatment of alcohol **370** with

one equivalent of Burgess reagent formed charged species **371** where the ketonic oxygen had undergone preferential reaction in the presence of the tertiary alcohol. Addition of a further equivalent of Burgess reagent with heating formed bis-adduct **372**, which underwent the desired elimination to provide dibenzylotonecine **373** after work-up. Lewis acid catalysed debenzylation completed the total synthesis of (*rac*)-otonecine in 20 steps overall. Vedejs commented that all the transformations in the presence of the tertiary amine and ketone were dominated by the transannular interaction, which complicated the use of electrophilic reagents in this "deceptively simple ring system".

In 1983, Ban and co-workers published an informative synthesis of the otonecine-type PA degradation product, (*rac*)-dihydrodeoxyotonecine.[241] The synthesis demonstrates how a N-C8 transannular interaction can dramatically influence the reactivity of the ring system. The synthesis began with the preparation of azocane **375** in six steps by annulation of diketone **374** (Scheme 82A).[241,242] Direct C7-oxidation of ketone **375** failed, partly due to the propensity of the lactam to ring open under strongly basic or acidic conditions. On the other hand, bromination of the C7-position of ketone **375** formed bromide **376** quantitatively, but subsequent S_N2-substitution of the bromide by NEt_4OAc failed due to competing E1cB elimination of the bromide (i.e. **377** was formed). To circumvent this, the lactam of **375** was first reduced by a three step sequence, including ketone protection as the dimethyl acetal and deprotection, to form amine **378**. However, subsequent C7-oxidation of amine **378** failed because of the N-C8 transannular interaction, which reduced the ketonic properties of the ketone.

In order to install the C7-alcohol of dihydrodeoxyotonecine in the absence of a transannular interaction, and without competing elimination reactions, the authors carried out a three step synthesis of carbamate **379** (Scheme 82B). The ketone of carbamate **379** reacted efficiently with bromine, and the following S_N2 reaction of **375** with sodium acetate proceeded in high yield to afford C7-acetate **390**. The synthesis of dihydrodeoxyotonecine was completed after a five step sequence of protection/deprotection and reduction/oxidation steps. Ban's studies highlight the difficulties in carrying out transformations on a functionally dense medium-sized ring and in the presence of the transannular interaction.

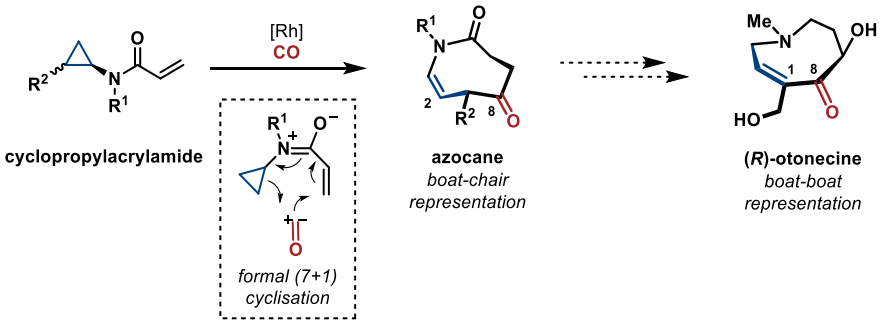


Scheme 82: A) *Reagents and conditions (some details were not provided by the authors)*: i) aq. K_2CO_3, MeOH, 50 °C to 60 °C, 81%; ii) Br_2, MeOH, quantitative; iii) Et_4NOAc, acetone, reflux, 90%; iv) $CH(OMe)_3$, H_2SO_4, MeOH, 63%; v) $LiAlH_4$, THF, reflux; vi) 50% aq. trifluoroacetic acid, 63% from **375**. B) *Reagents and conditions*: i) $CH(OMe)_3$, H_2SO_4, MeOH; ii) $LiAlH_4$, THF, reflux; iii) CbzCl, $CHCl_3$, reflux, 81% from **375**; iv) Br_2, MeOH; v) Et_4NOAc, acetone, reflux, 83% from **379**; vi) NH_3, MeOH, r.t.; vii) 2,3-dihydropyran, CSA, CH_2Cl_2; viii) $LiAlH_4$, THF, reflux; ix) PCC, CH_2Cl_2, NaOAc; x) HCl, MeOH, r.t., 30% from **390**.

3.1.3 Rh(I)-catalysed (7+1) carbonylative cycloaddition approach to the total synthesis of otonecine

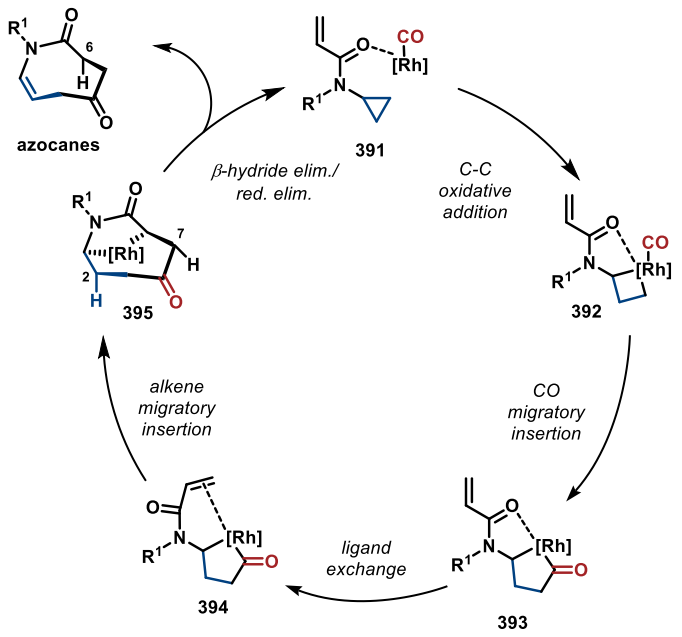
Note: Due to the well-documented importance of the 3-dimensional structure of medium-sized rings on their reactivity and the selectivity of their transformations, azocane rings contained in the remainder of this thesis will be depicted in 3-D. Therefore, C2-unsaturated azocanes will be depicted in the boat-chair conformation (see azocane, Scheme 83*) and C1-unsaturated azocanes will be depicted in a boat-boat conformation like that of otonecine (see* Scheme 83*). Further evidence for the predominance of these conformations is provided by computational studies described in Chapter 3.2.3.2.*

As part of the ongoing project at Bristol developing rhodacyclopentanone-based methodologies for the synthesis of sp^3-rich heterocycles, Dr Megan Shaw published the Rh(I)-catalysed (7+1) carbonylative cyclisation of cyclopropylacrylamides to form azocanes.[101] The azocanes produced in this reaction bear several structural similarities to otonecine, which suggests that they might serve as intermediates in its total synthesis (Scheme 83). For example, the ketone of these azocanes is in the correct position relative to the amine, the azocanes are unsaturated in the C2-C3 position, which is one position away from the C1-C2 alkene in otonecine, and alkyl C1-substituents can be incorporated (perhaps enantioselectively) when 1,2-disubstituted cyclopropyl substrates are employed.



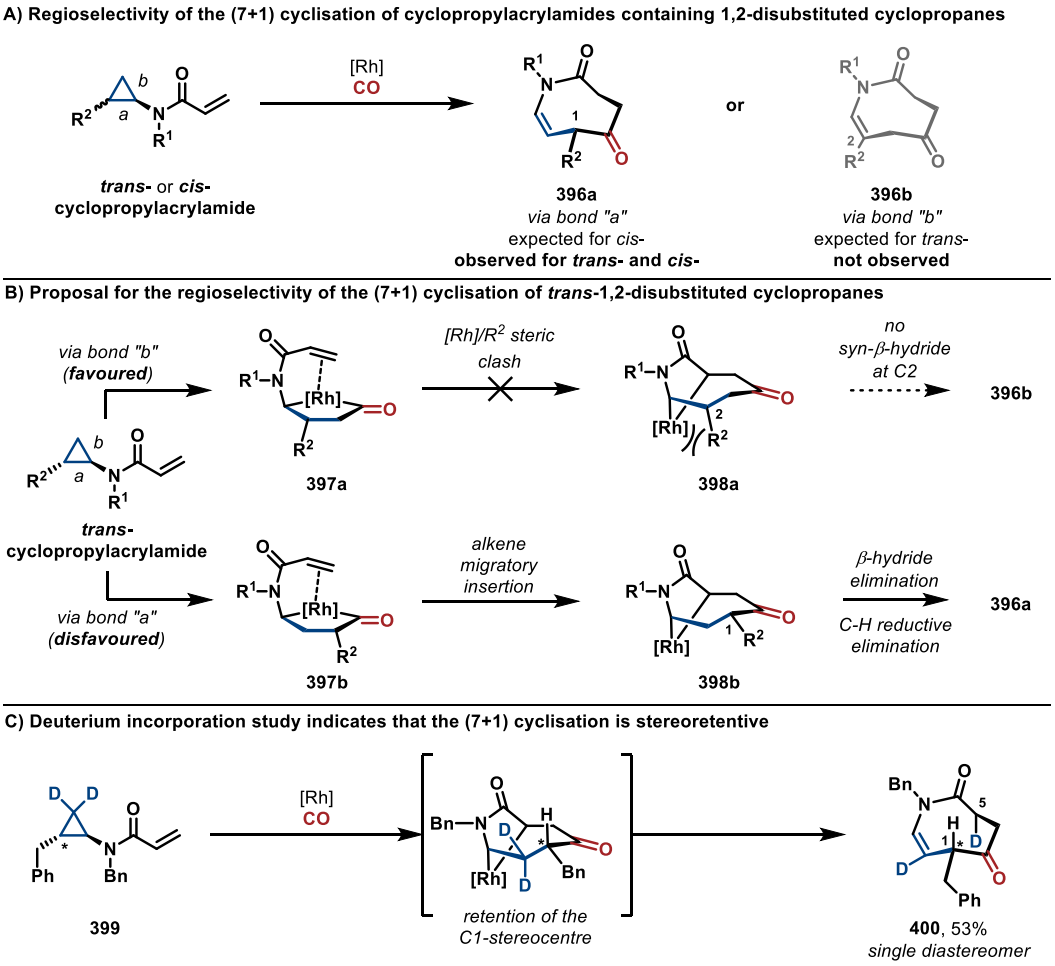
Scheme 83: Structural similarities between azocanes produced in the (7+1) carbonylative cyclisation and otonecine.

The proposed mechanism of the (7+1) carbonylative cyclisation begins in an identical manner to the methodologies presented in Section 1.3 and Chapter 2. A cationic Rh(I)-catalyst undergoes carbonyl-directed oxidative addition to the proximal cyclopropyl C-C bond of cyclopropylacrylamides **391** to form rhodacyclobutane **392** (Scheme 84). CO migratory insertion then forms rhodacyclopentanone **393**. Upon coordination to the rhodacyclopentanone, the alkene undergoes migratory insertion into the Rh(III)-acyl bond of **394** to give bridged intermediate **395**. β-Hydride elimination takes place exclusively from the C2 position (versus C7), and C-H reductive elimination forms the azocane with regeneration of the Rh(I)-catalyst.



Scheme 84: Mechanism of the Rh(I)-catalysed (7+1) carbonylative cyclisation of cyclopropylacrylamides.

In the processes discussed in Section 1.3 and Chapter 2, cyclopropane-based substrates containing 1,2-disubstituted cyclopropanes reacted in a regiodivergent manner depending on whether the *trans*- or *cis*-diastereomer of the substrate was employed.[99, 102] However, in the (7+1) carbonylative cyclisation, cyclopropylacrylamides containing *trans*- or *cis*-1,2-disubstituted cyclopropanes both reacted *via* Rh(I)-addition to the more substituted C-C bond "*a*" resulting in the sole formation of C1-substituted azocanes **396a** (Scheme 85A). This is fortunate because it might allow the C1-hydroxymethyl substituent of otonecine to be incorporated during the (7+1) carbonylative cyclisation of either *trans*- or *cis*-1,2-disubstituted cyclopropylacrylamides. The regioselectivity of the (7+1) carbonylative cyclisation of *trans*-1,2-disubstituted cyclopropylacrylamides was reasoned by considering alkene migratory insertion into the two possible rhodacyclopentanone intermediates **397a** and **397b** (Scheme 85B). Based on previously described studies, Rh(I)-addition is selective for the less-substituted C-C bond "*b*" of *trans*-1,2-disubstituted cyclopropanes (Section 1.3.3). However, alkene migratory insertion into the resulting rhodacyclopentanone **397a** is accompanied by a developing steric repulsion between the Rh(III)-centre and R^2-substitutent (see intermediate **398a**). Furthermore, resulting [Rh]-azocane **398a** does not possess a *syn*-β-hydride to the Rh(III)-moiety for β-hydride elimination. As has previously been discussed, rhodacyclopentanone formation is completely reversible, therefore, **397a** can revert to the starting material, and Rh(I)-addition to the disfavoured C-C bond "*a*" can take place resulting in the formation of rhodacyclopentanone **397b**. Now, alkene migratory insertion into **397b** is favourable because of the absence of a developing steric interaction, so bridged intermediate **398b**, and consequently C1-substituted azocane **396**, are formed. The regioselectivity observed for *cis*-1,2-disubstituted cyclopropanes in the (7+1) carbonylative cyclisation (i.e. *via* more substituted C-C bond "*a*") is expected based on previous studies.[102]



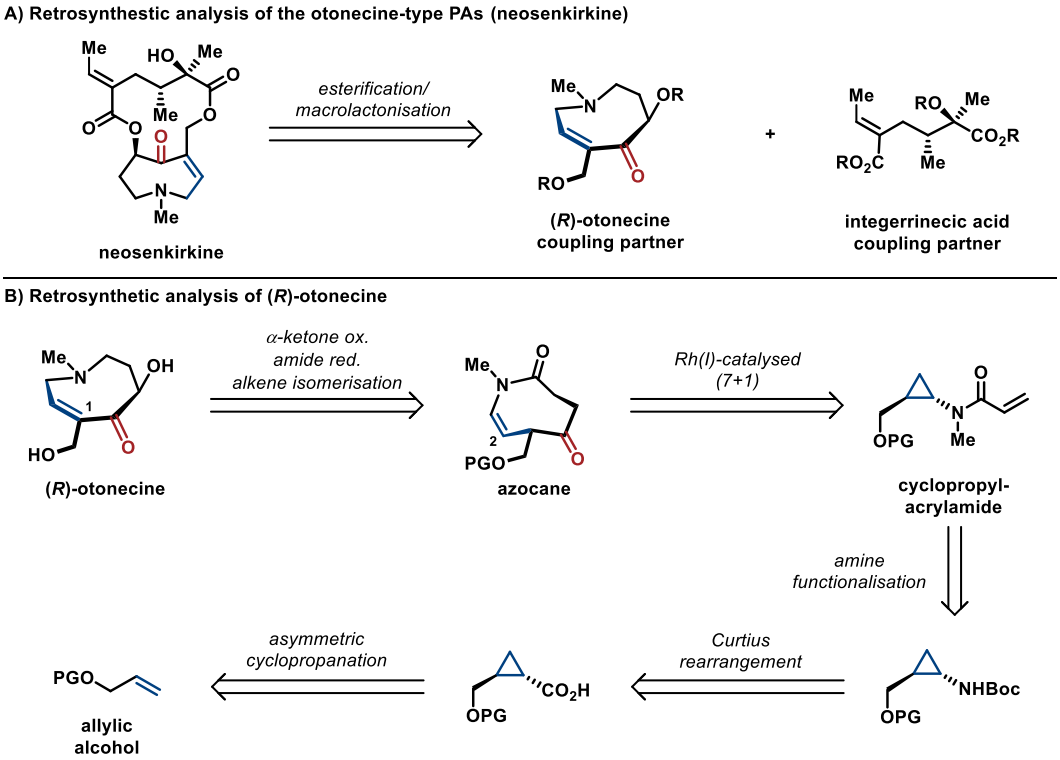
Scheme 85

Shaw also showed that the (7+1) carbonylative cyclisation of *trans*-1,2-disubstituted cyclopropanes is stereoretentive whereby the relative stereochemistry of 1,2-disubstituted cyclopropanes is retained in the product azocanes. This was confirmed by cyclisation of deuterated substrate **399**, which formed **400** as a single diastereomer (Scheme 85C). Stereoretention in rhodacyclopentanone-based methodologies, developed at Bristol, has been demonstrated in related methodologies (Section 2.1.3.2).[103] The ability to access azocanes in high enantiopurity by this method is important for the planned total synthesis of (*R*)-otonecine.

Studies towards the total synthesis of otonecine were undertaken at Bristol for several reasons. The otonecine-type PAs possess potent biological activities and interesting physical chemical properties because of the N-C8 transannular interaction, and so synthetic access to these compounds might aid investigations into their therapeutic potential. Also, the unique azocane ring structure and presence of the transannular interaction make otonecine a synthetically challenging target, which is highlighted by the fact that none of the otonecine-type PAs have previously been synthesised. Finally, lessons learned by applying a rhodacyclopentanone-based methodology developed at Bristol to a total synthesis might benefit the development of related methodologies.

At the outset, it was planned that the otonecine-type macrocyclic diesters would be formed by the union of an otonecine and necic acid building block by a sequence of esterification and macrolactonisation reactions (Scheme 86A). Literature precedent for this esterification/macrolactonisation strategy will be presented in Section 3.3.1 along with previous synthesis of necic acids.

A simple retrosynthetic analysis of (*R*)-otonecine is presented in Scheme 86B. The planned synthesis hinges on gaining access to a suitably functionalised, enantioenriched azocane by (7+1) carbonylative cyclisation of an enantioenriched cyclopropylacrylamide. The exact identity of the cyclopropylacrylamide was not certain because it was not clear if substrates bearing *N*-methyl or hydroxymethyl-substituted cyclopropanes would be tolerated in the (7+1) carbonylative cyclisation. Nevertheless, it was proposed that the cyclopropylacrylamide could be accessed from a protected allyl alcohol *via* asymmetric cyclopropanation and Curtius rearrangement. Depending on the optimal azocane, the final steps in the total synthesis of (*R*)-otonecine would require a diastereoselective α-ketone oxidation, lactam reduction and isomerisation of the alkene from C2 to C1.



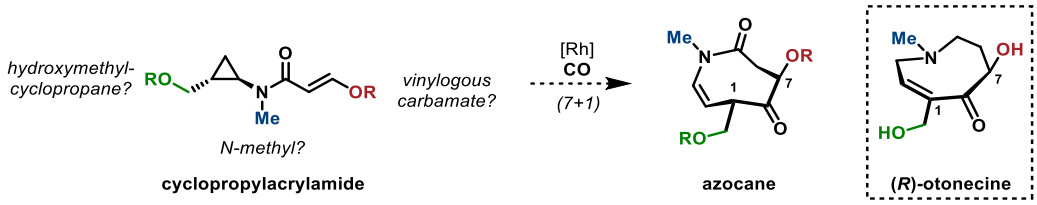
Scheme 86

3.2 Studies towards the total synthesis of otonecine

3.2.1 Studies into the (7+1) carbonylative cycloaddition

3.2.1.1 Identification of a suitable (7+1) substrate

Synthetic studies towards the total synthesis of otonecine began with the identification of a suitable (7+1) carbonylative cycloaddition substrate. This required reinvestigation of the scope of the cycloaddition because certain substrate functionalities, which were deemed vital to the success of the project, were not considered in the original publication. Firstly, it was not known whether *N*-methyl cyclopropylacrylamides (indicated in blue) would be tolerated (Scheme 87). This addition to the scope was vital to the success of the project because it would avoid the need to carry out wasteful *N*-functionalisations at a late-stage in the synthesis. Secondly, cyclisation of 1,2-disubstituted hydroxymethylcyclopropanes (indicated in green) would dramatically increase the efficiency of the proposed synthesis by incorporating the C1-hydroxymethyl moiety of otonecine during the (7+1) carbonylative cycloaddition. This class of 1,2-disubstituted cyclopropane had not been investigated in any of the rhodacyclopentanone-based methodologies developed at Bristol, so it was not clear if this would be successful. Finally, investigations would be carried out into cycloaddition substrates containing a vinylogous carbamate (indicated in red) because these might give access to C7-hydroxy azocanes, thus removing the need for an α-ketone oxidation step. As described below, these issues regarding the scope of the (7+1) carbonylative cycloaddition were addressed by synthesising model acrylamide substrates and subjecting them to the (7+1) carbonylative cycloaddition conditions.

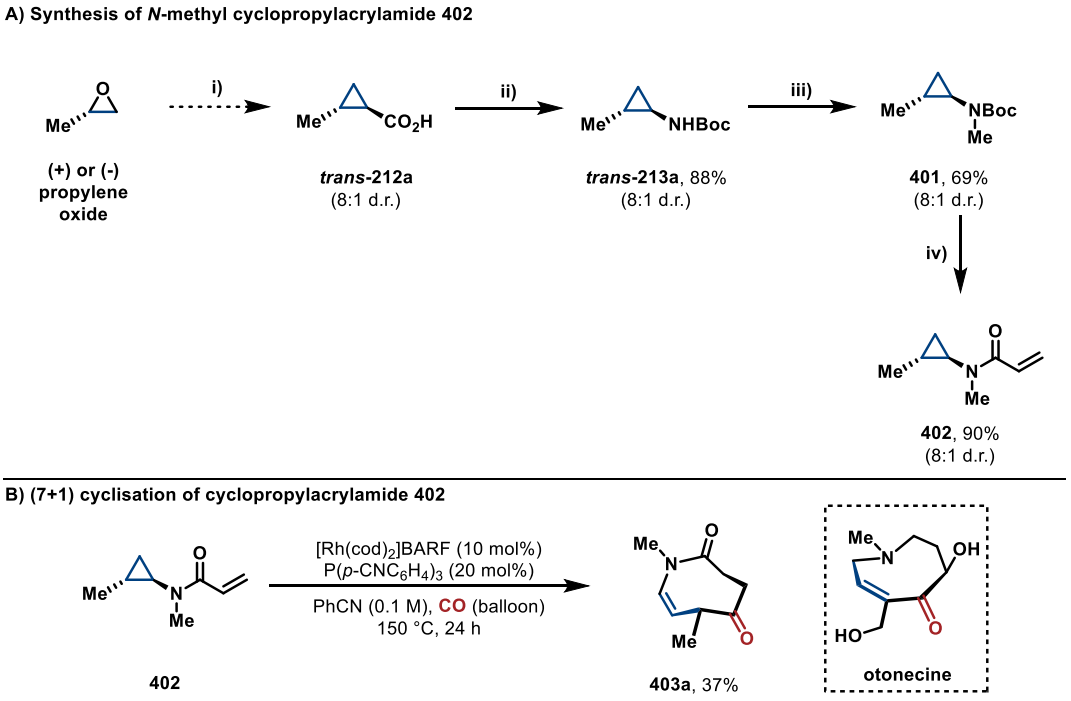


Scheme 87: Desirable additions to the scope of the (7+1) carbonylative cycloaddition.

Acrylamide **402** was initially targeted in order to investigate whether *N*-methyl substitution was tolerated under the (7+1) carbonylative cycloaddition conditions (Scheme 88A). Following a route previously published by the Bower group, commercially available carboxylic acid ***trans*-212a** (8:1 d.r.) underwent Curtius rearrangement with diphenylphosphoryl azide in *t*-BuOH to form Boc-protected amine ***trans*-213a** (88%, 8:1 d.r.).[102] *N*-Methylation using sodium hydride and iodomethane was straightforward generating carbonate **401** in 69% yield. The Boc-protecting group was removed on treatment with trifluoroacetic acid, and the resulting amine-TFA salt was reacted with acryloyl chloride to form acrylamide **402** (90%, 8:1 d.r.). This one-pot deprotection/acrylamide formation of Boc-protected amines avoids the need to isolate the potentially volatile amine free base. Note that

enantioenriched carboxylic acid **(*S*,*S*)-212a** (both enantiomers are accessible) can be prepared in one step by a Horner-Wadsworth-Emmons cyclopropanation using enantiomerically pure propylene oxide.[154]

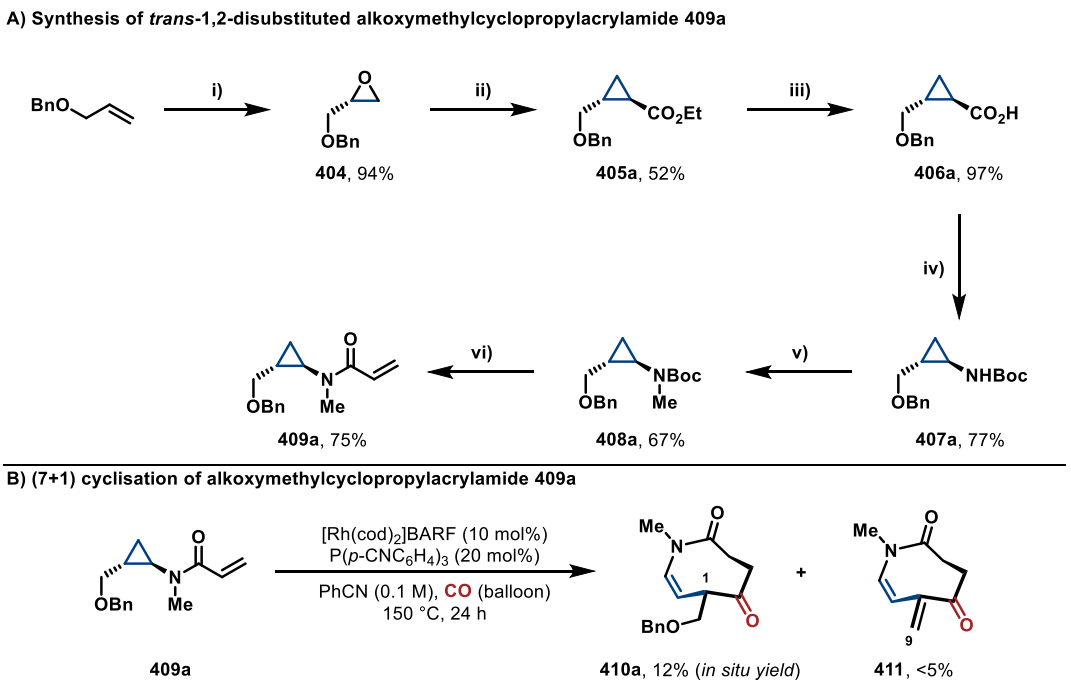
Having prepared *N*-methyl substituted cyclopropylacrylamide, it was subjected to the (7+1) carbonylative cycloaddition conditions. When reacted with a $[Rh(cod)_2]BARF/P(p\text{-}CNC_6H_4)_3$ catalyst system in benzonitrile under a CO atmosphere, cyclopropylacrylamide **402** formed azocane **403a** in 37% yield, as a single regioisomer (Scheme 88B). Azocane **403a** was considered a viable intermediate in the synthesis of (*R*)-otonecine because it contains the complete carbon skeleton of the natural product and is potentially available in an enantioenriched form. Therefore, this result served as validation of the retrosynthesis in Scheme 86B.



Scheme 88: A) *Reagents and conditions*: i) Literature conditions: TEPA, HexLi, MeTHF, 150 °C, 18 h; ii) diphenylphosphoryl azide, NEt_3, *t*-BuOH, 80 °C, 72 h, 88%, 8:1 d.r.; iii) NaH, MeI, THF, r.t., 16 h, 69%, 8:1 d.r.; iv) trifluoroacetic acid, CH_2Cl_2, r.t., 30 min *then* acryloyl chloride, K_2CO_3, acetone-water, 0 °C to r.t., 16 h, 90%, 8:1 d.r..

Next, acrylamide **409a**, containing a benzyl-protected 1,2-disubstituted hydroxymethylcyclopropane, was synthesised to investigate whether substrates of this type would allow installation of the C1-hydroxymethyl group of otonecine during the (7+1) carbonylative cycloaddition step (Scheme 89A). Ally benzyl ether underwent high yielding epoxidation to provide epoxide **404** in 94% yield, which was subjected to Horner-Wadsworth-Emmons cyclopropanation using TEPA, to form ester **405a** as a single diastereomer in 52% yield. Ester hydrolysis provided carboxylic acid **406a** (97%), which was advanced to cyclopropylacrylamide **409a** by *N*-methylation (67%) and a one-pot Boc-

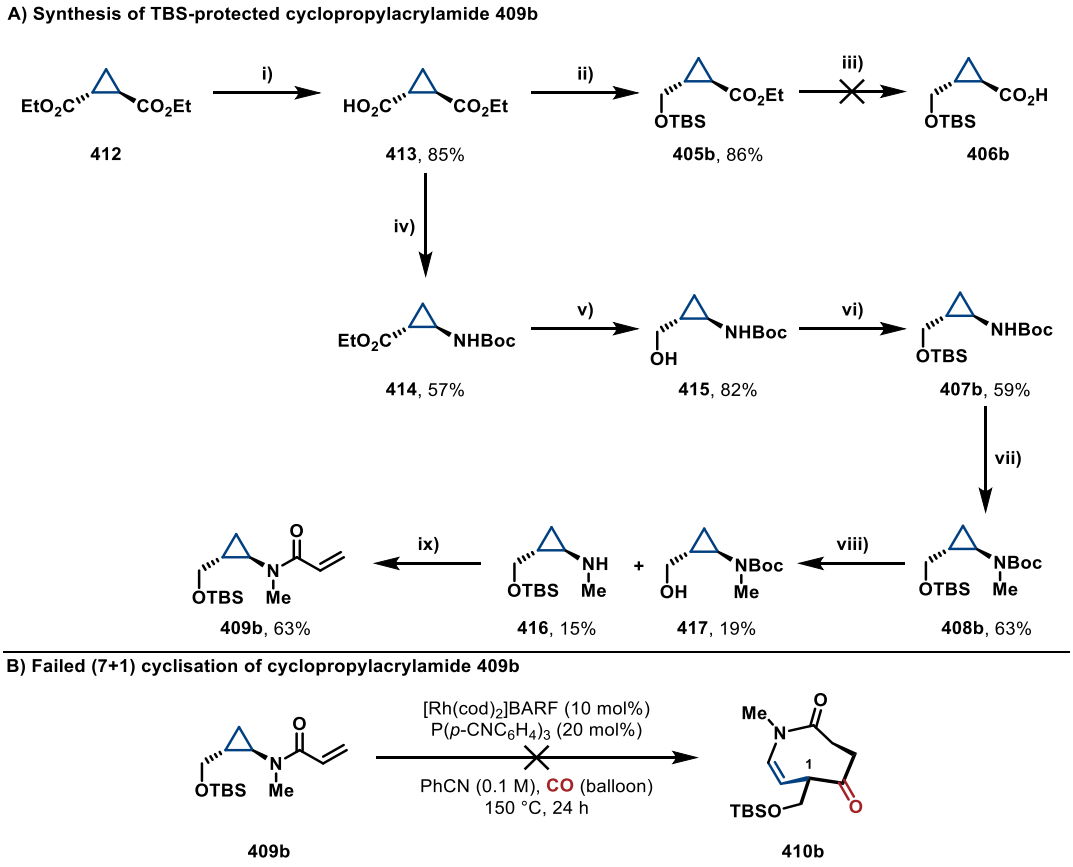
deprotection/acrylamide formation sequence (75%). When subjected to the (7+1) carbonylative cycloaddition conditions, C1-alkoxymethyl azocane **410a** was formed, but was observed to degrade over time under the reaction conditions (Scheme 89B). As a result of its instability, azocane **410a** could only be formed in 12% yield. Evidence for the mechanism of degradation of C1-alkoxymethyl azocane **410a** was provided by the tentative identification of alkene **411** in the crude reaction mixture. Alkene **411** is likely formed by thermal elimination of the alkoxy-substituent of azocane **410a**. Brief efforts to avoid deleterious elimination from azocane **410a** failed to improve the yield of the (7+1) carbonylative cycloaddition, so studies involving acrylamide **409a** were abandoned.



Scheme 89: A) *Reagents and conditions*: i) *m*-CPBA, CH_2Cl_2, r.t., 16 h; ii) triethyl phosphonoacetate, NaH, 1,2-DME, 0 °C to reflux, 24 h; iii) aq. 4 M NaOH, MeOH, r.t., 16 h; iv) diphenylphosphoryl azide, NEt_3, *t*-BuOH, 80 °C, 22 h; v) NaH, MeI, THF, r.t., 1 h; vi) trifluoroacetic acid, CH_2Cl_2, r.t., 30 min *then* acryloyl chloride, K_2CO_3, acetone-water, 0 °C to r.t., 16 h.

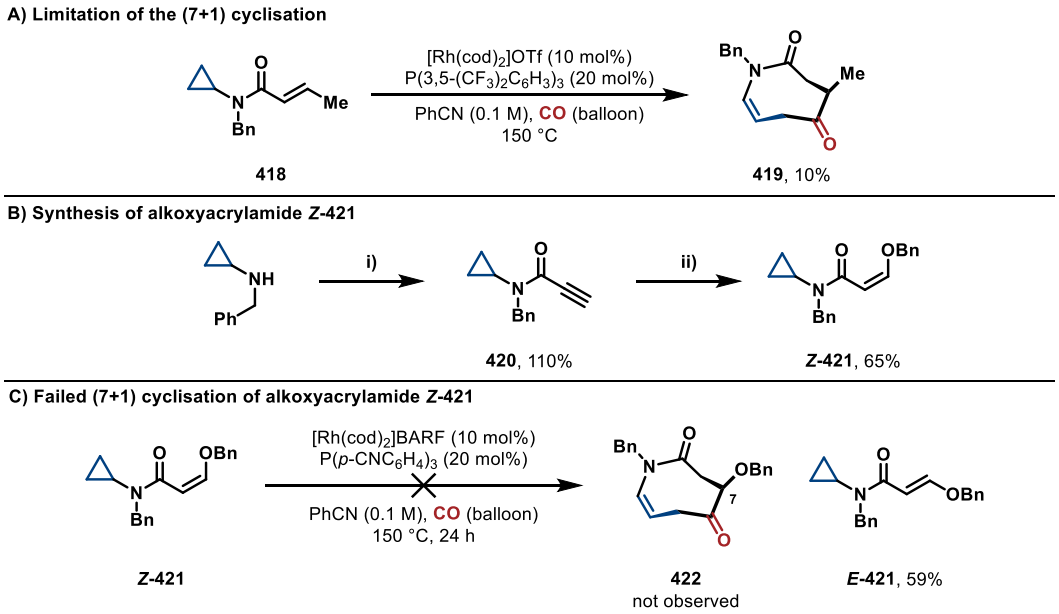
In order to improve the stability of C1-alkoxymethyl azocanes, it was proposed that a more electron donating *O*-protecting group might disfavour *O*-elimination by destabilising the resulting alkoxide. Therefore, acrylamide **409b** was synthesised and tested in the (7+1) carbonylative cycloaddition (Scheme 90A). The synthesis began with commercially available diester **412**, which underwent mono-hydrolysis when treated with one equivalent of base to generate carboxylic acid **413** in 94% yield. Chemoselective borane reduction and TBS-protection of the resulting alcohol provided ester **405b** in 86% yield over the two steps. Hydrolysis of the ester proceeded smoothly, but resulting silyl ether **406b** was sensitive to desilylation upon acidification during the work-up, so an alternative step order was investigated to form acrylamide **409b**.

The synthetic sequence was reordered such that carboxylic acid **413** underwent Curtius rearrangement to give Boc-protected amine **414** in 57% yield, the ester of which was reduced using DIBAL-H to form alcohol **415** in 82% yield. The alcohol was TBS-protected in 59% yield, and *N*-methylation formed carbamate **408b** in 63% yield. The following Boc-deprotection step was carried out using $ZnBr_2$ because of the observed sensitivity of TBS-protected alcohol **406b** to Brønsted acids.[243] However, treatment of carbamate **408b** with $ZnBr_2$ provided both Boc-deprotected amine **416** and TBS-deprotected alcohol **417** in 15% and 19% yields, respectively. Despite the disappointing yield of the Boc-deprotection step, amine **416** was treated with acryloyl chloride to yield the target acrylamide **409b** in 63% yield. Under the (7+1) carbonylative cycloaddition, acrylamide **409b** underwent non-specific degradation and target azocane **410b** was not observed (Scheme 90B). Further studies into the (7+1) carbonylative cyclisation of substrates containing 1,2-disubstituted hydroxymethylcyclopropanes were abandoned due to the instability of the resulting azocanes. Instead, attempts would be made to install the C1-hydroxymethyl substituent of otonecine by late-stage C-H oxidation of the C1-methyl group. These studies are presented in Section 3.2.4.



Scheme 90: A) *Reagents and conditions*: i) aq. 4 M NaOH, EtOH, r.t., 4 h; ii) BH_3.THF, THF, 0 °C to r.t., 16 h *then* TBSCl, imidazole, DMF, r.t., 3 h; iii) aq. 4 M NaOH, MeOH, r.t., 16 h; iv) diphenylphosphoryl azide, NEt_3, *t*-BuOH, 80 °C, 24 h; v) DIBAL, PhMe, -78 °C, 3 h; vi) TBSCl, imidazole, DMF, r.t.; vii) NaH, MeI, THF, r.t., 16 h; viii) $ZnBr_2$, CH_2Cl_2, r.t., 16 h; ix) acryloyl chloride, K_2CO_3, acetone-water, 0 °C to r.t., 16 h.

In the original investigations into the scope of the (7+1) carbonylative cycloaddition, Shaw observed that β-methylacrylamide **418** cyclised to form C7-methyl azocane **419** in 10% yield (Scheme 91A).[101] Despite this, cyclopropylacrylamide ***Z*-421**, containing a vinylogous carbamate, was synthesised in order to access C7-hydroxyazocane **422** (Scheme 91B). The synthesis was achieved by coupling benzylcyclopropylamine and propiolic acid with DCC to form amide **420** in quantitative yield. Then *Z*-selective 1,4-addition of benzyl alcohol was achieved with catalytic silver(I) triflate to form desired *Z*-acrylamide ***Z*-421**in 65% yield.[244] Treatment of acrylamide ***Z*-421** under the (7+1) carbonylative cycloaddition conditions did not form azocane **422**, but caused the isomerisation of the alkene to form *E*-acrylamide ***E*-421** (Scheme 91C). The failure to form azocane **422** also suggested that *E*-acrylamides were not suitable (7+1) carbonylative cycloaddition substrates, so investigations into this class of substrate were halted.



Scheme 91: B) *Reagents and conditions*: i) propiolic acid, DCC, DMAP, CH_2Cl_2, 0 °C to r.t., 2 h; ii) AgOTf, BnOH, 70 °C, 3 h.

The studies into the model substrates above identified *N*-methyl cyclopropylacrylamide **402** and azocane **403a** as viable intermediates for the total synthesis of otonecine. Efforts were then directed towards optimising the (7+1) carbonylative cycloaddition of cyclopropylacrylamide **402** such that the reaction could be carried out efficiently on a larger scale. This would allow the remaining transformations in the synthesis to be investigated.

3.2.1.2 Optimisation of the (7+1) carbonylative cycloaddition

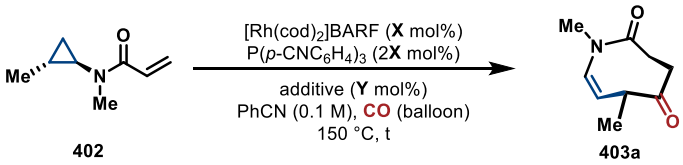
Based on the results of the previous section, acrylamide **402** was chosen as a substrate for further optimisation, and selected results are shown in Table 12. The conditions developed by Shaw formed azocane **403a** in a moderate 35% yield on 0.15 mmol scale with 10 mol% of $[Rh(cod)_2]BARF$

and 20 mol% of P(*p*-CNC_6H_4)$_3$ (Table 12, Entry 1). Optimisation studies were undertaken with the goal of increasing the yield of azocane **403a**, whilst reducing the catalyst and ligand loadings. The scale of the reaction would also need to be increased to facilitate studies on the remaining transformations.

Initially, a screen of commercially available mono- and bidentate phosphines, triarylarsines, phosphites, sulfur-based ligands, and *N*-heterocyclic carbenes was carried out in combination with a cationic Rh(I)-catalyst, but this failed to identify a ligand superior to P(*p*-CNC_6H_4)$_3$. The first significant increase in yield of azocane **403a** was achieved by including benzamide as an additive, which provided azocane **403a** in 43% yield (Entry 2). Amide and carboxylic acid additives have provided a beneficial effect in related Rh(I)-catalysed carbonylative cycloadditions developed at Bristol.[102-103, 105] Subsequently, a screen of Lewis-basic additives identified sulfonamides and carboxylic acids as beneficial additives. For example, *p*-toluenesulfonamide and pivalic acid provided azocane **403a** in 40% and 49% yield, respectively (Entries 3 and 4). Interestingly, the tertiary amide, dimethylacetamide, also provided a substantial improvement when compared to benzamide, which suggests that an acidic proton is not vital for the beneficial effect of the additive (Entry 6). This finding apparently conflicts with the observation that trifluoroacetamide (48% yield, Entry 5) was also more effective than benzamide. Ultimately, the secondary amide, *N*-methyltrifluoroacetamide, was identified as a suitable additive, which provided azocane **403a** in 51% yield (Entry 7). The role of amide/carboxylic acid additives in these reactions is unknown. It was observed empirically that Lewis-basic additives caused the reaction mixture to remain as a homogeneous solution and postponed the precipitation of Rh-black. This might indicate that Lewis-basic additives play a role in stabilising Rh-species in solution. The observation that dimethylacetamide (Entry 6) provided a beneficial effect suggest that the amide might be acting as a Lewis base, and not as a source of protons or as a hydrogen bond donor.

Having identified improved reaction conditions that provided azocane **403a** in 51% yield on a 0.15 mmol scale, investigations were directed towards increasing the scale of the reaction. When the reaction was carried out on a 0.50 mmol scale, the yield of azocane **403a** fell to 41% under otherwise identical conditions (Entry 8). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated that the phosphine ligand, P(*p*-CNC_6H_4)$_3$, was no longer present. It was discovered that the phosphine ligand had been oxidised to the corresponding phosphine oxide, presumably by reaction with oxygen during the (7+1) carbonylative cycloaddition. Similar oxidation processes are catalysed by various transition metals.[245-246] This reactivity is likely to have caused the reaction to lose efficiency, resulting in the reduced yield. It was proposed that the use of balloons to apply a CO atmosphere might also allow the introduction of oxygen into the reaction over time by diffusion through the rubber wall. Therefore, in order to minimise the amount of oxygen in the reaction, a more rigorous method of applying a CO atmosphere was investigated. This was achieved by performing the reaction in a sealed Schlenk tube under a CO atmosphere, which was set up *via* a three-way cylinder head attached to a Schlenk-line and CO cylinder (*Further details are available in the Experimental section*). When this new set up was

employed, azocane **403a** was formed in 51% yield on a 0.50 mmol scale (Entry 9). Furthermore, the new reaction set up increased the lifetime of the active catalytic species, which in turn allowed a reduction in both the Rh(I)-catalyst and ligand loadings whilst also providing a modest increase to the yield of azocane **403a** (54% yield, Entry 10).



402 **403a**

Entry	Scale	X	Additive	Y	time	Yield[a]
1	0.15 mmol	10	-	-	24 h	35%
2	0.15 mmol	10	benzamide	150	24 h	43%
3	0.15 mmol	10	*p*-toluenesulfonamide	100	24 h	40%
4	0.15 mmol	10	pivalic acid	100	24 h	49%
5	0.15 mmol	10	trifluoroacetamide	100	24 h	48%
6	0.15 mmol	10	dimethylacetamide	100	24 h	46%
7	0.15 mmol	10	*N*-methyltrifluoroacetamide	100	24 h	51%
8	0.50 mmol	10	*N*-methyltrifluoroacetamide	100	24 h	41%
9[b]	0.50 mmol	10	*N*-methyltrifluoroacetamide	50	24 h	51%
10[b]	1.00 mmol	**5**	*N*-methyltrifluoroacetamide	**50**	**70 h**	**54%**

[a]*In-situ* NMR yield measured against an internal standard; [b]Reaction performed in a sealed tube.

Table 12: Selected results from the optimisation of the (7+1) carbonylative cycloaddition of cyclopropylacrylamide **402**.

The newly optimised conditions for the Rh(I)-catalysed (7+1) carbonylative cycloaddition of acrylamide **402** enable the reaction to be run routinely on a multi-mmol scale. This allowed the focus of the investigations to shift towards the remaining transformations in the total synthesis of otonecine. Further optimisation of the (7+1) carbonylative cycloaddition of cyclopropylacrylamide **402** should be directed towards identifying the optimum additive for this transformation. Elucidating the exact role of these additives may allow the rational design of an improved catalyst system applicable to related reactions.

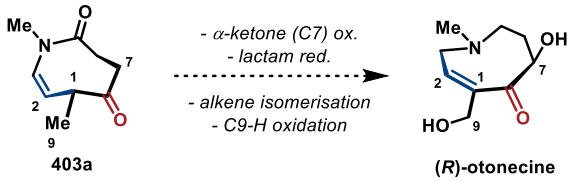
3.2.2 The post-cycloaddition transformations

The optimised conditions for the (7+1) carbonylative cycloaddition of cyclopropylacrylamide **402** provided suitable quantities of viable intermediate azocane **403a**, which facilitated further investigations into the post-cycloaddition transformations towards the total synthesis of otonecine. The four post-cycloaddition transformations included (Scheme 92): 1) oxidation of the C7-position by a

diastereoselective α-ketone oxidation; 2) lactam reduction; 3) alkene isomerisation from the C2 to the C1-position; 4) C-H oxidation of the C9-position. At the outset of the project, it was unclear in what order the post-cycloaddition transformations should be carried out, however, three assumptions were made:

- The C7-alcohol of otonecine should be installed by diastereoselective α-ketone oxidation before alkene isomerisation to the C1-position, in order to transfer the C1-stereochemistry.
- The lactam reduction should be carried out towards the end of the synthesis to limit potential complications due to the transannular interaction.
- The C9-alcohol of otonecine might be installed by an allylic oxidation, so should be carried out after alkene isomerisation to the C1-position.

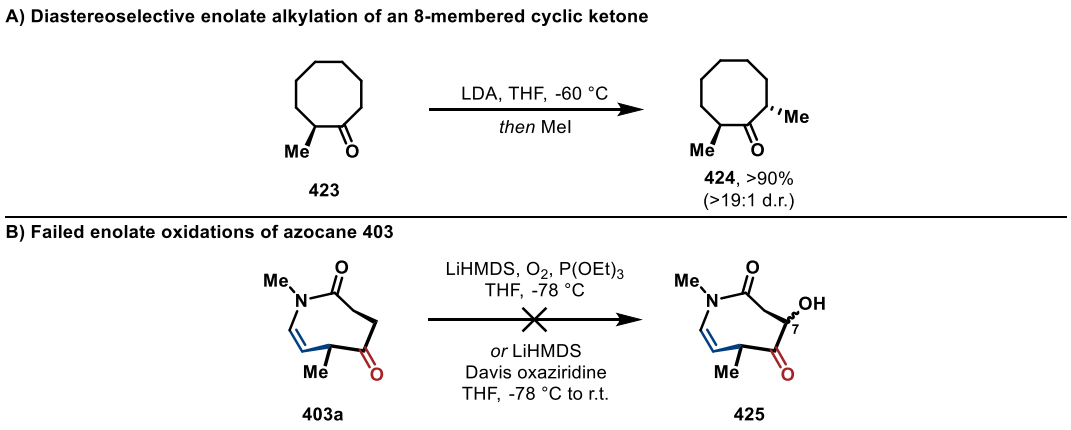
The following studies aimed to identify suitable means of carrying out the remaining transformations and to provide further information regarding a suitable order of steps.



Scheme 92: Post-cycloaddition transformations required in the synthesis of otonecine.

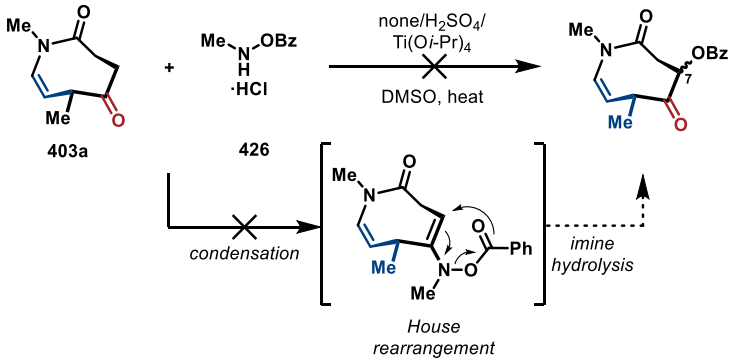
3.2.2.1 α-Ketone oxidation

The first post-cycloaddition transformation to be attempted was the diastereoselective α-ketone oxidation because it was likely to be the first post-cycloaddition transformation in the total synthesis of otonecine. Previously, Still and Galynker reported that eight-membered cyclic ketone **423** underwent highly regio- and diastereoselective alkylation under kinetic conditions, which favoured the formation of *trans* dialkylketone **424** (Scheme 93A).[247] It was hoped that the C7-oxidation of azocane **403a**, under similar conditions, might also proceed with high levels of regio- and diastereoselectivity. Therefore, initial attempts were made to oxidise the C7-position of azocane **403a** in a single step by oxidation of the metal enolate. Azocane **403a** was deprotonated with LiHMDS under cryogenic conditions, and the resulting lithium enolate was reacted directly with molecular oxygen and $P(OEt)_3$, or Davis oxaziridine, but no C7-oxidised products were formed (Scheme 93B).



Scheme 93

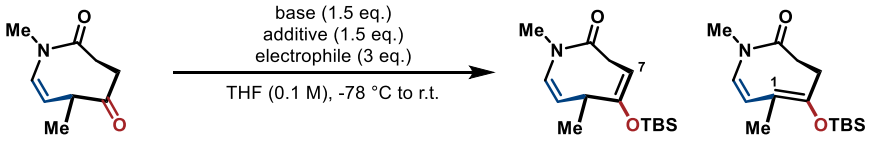
An alternative one-pot method for carrying out the C7-oxidation was briefly investigated. Tomkinson and co-workers have reported several acyl-oxime reagents that can react with ketones to form α-acyl ketones *via* House rearrangement of the intermediate enamines (Scheme 94).[248-252] However, acyl-oxime **426** could not be condensed onto the ketone of azocane **403a**, even in the presence of strong Brønsted and Lewis acids, so this method was abandoned.



Scheme 94: Failed C7-acetylation of azocane **403a** by a House rearrangement.

Having failed to install the C7-alcohol onto azocane **403a** by direct oxidation of a metal enolate, a two step Rubottom oxidation sequence was attempted, which required highly regioselective conditions for the formation of TBS-silyl enol ether **427a**. The TBS-group was chosen so that it might act as a protecting group for the C7-alcohol in subsequent transformations. To begin, azocane **403a** was added to an excess of LiHMDS, and the resulting lithium enolate was quenched with TBSCl to provide silyl enol ether **427a** in 59% yield, but as a mixture of regioisomers (5:2 **427a**:**427b**) (Table 13, Entry 1). When freshly prepared LDA was employed, an improved product ratio was afforded (41%, 25:1 **427a**:**427b**), but this result was irreproducible (Entry 2). Deprotonation of azocane **403a** at -78 °C was observed to be immediate (accompanied with the formation of a yellow colour) but subsequent reaction with TBSCl was slow at room temperature, which presumably allowed the lithium enolate to isomerise. Therefore, attempts were made to increase the rate of silylation by using TIPSOTf, as a more

electrophilic silylating reagent,[253] but this failed to form **427a** (Entry 3). Next, additives were trialled in an attempt to improve the regioselectivity of silyl enol ether formation by dissuading the formation of lithium aggregates.[254-255] When LiCl was added, degradation was observed (Entry 4), but the addition of DMPU was found to significantly increase the rate of silylation at room temperature, providing **427a** in 70% yield and 8:1 r.r in favour of the desired silyl enol ether (Entry 5).



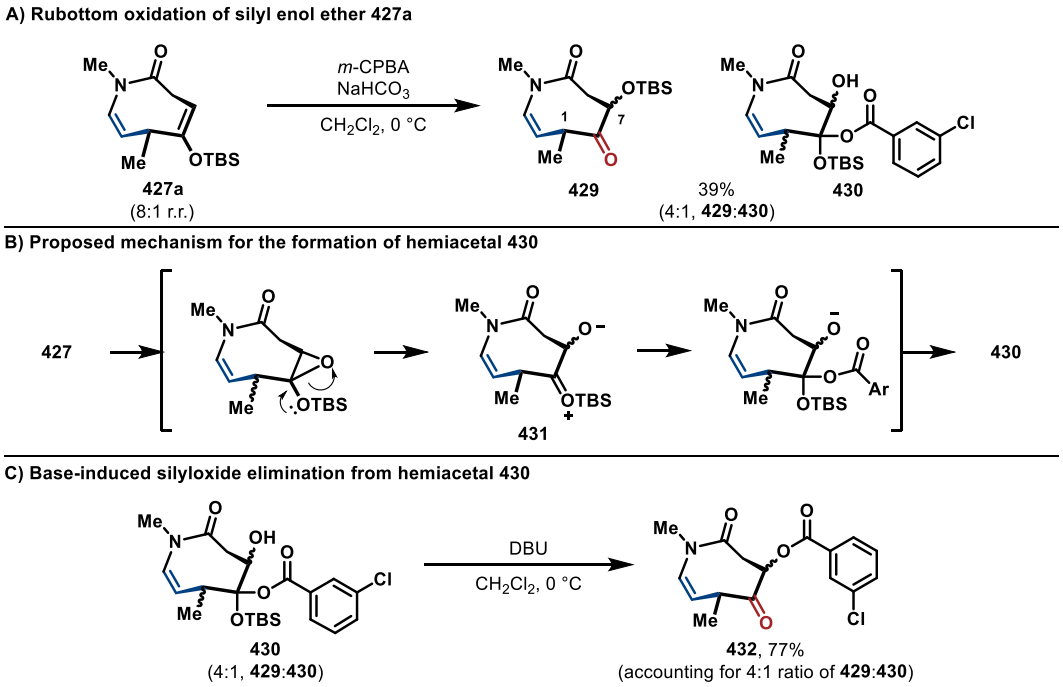
403a 427a 427b

Entry	Base	Additive	Electrophile	Yield	Ratio (427a:427b)
1	LiHMDS	-	TBSCl	59%	5:2
2	LDA	-	TBSCl	41%	25:1[a]
3	LDA	-	TIPSOTf	-	-
4	LDA	LiCl	TBSCl	degraded	-
5	**LDA**	**DMPU**	**TBSCl**	**70%**	**8:1**

[a]result was irreproducible

Table 13: Selected results from the optimisation of the synthesis of silyl enol ether **427a**.

Having gained reliable access to silyl enol ether **427a**, the Rubottom oxidation was attempted. Under basic-buffered conditions, *m*-CPBA reacted with silyl enol ether **427a** to form desired C7-siloxy ketone **429** as a single diastereomer, but as an inseparable mixture with acetal **430** (39% combined yield, 4:1 **429**:**430**) (Scheme 95A). Acetal **430** is likely formed by addition of *m*-chlorobenzoate to oxonium species **431** (Scheme 95B). Acetal **430** could not be separated from C7-silyloxide **429** by column chromatography or by aqueous work-up, but could be removed after treatment with DBU, which formed C7-benzoate **432** in 77% yield by acetyl migration and elimination of the C8-silyloxy group (Scheme 95C). It should be noted that the relative stereochemistry of the C1- and C7-positions of **429** (not determined at this point) is inconsequential because the C1-stereocentre will be removed later in the synthesis upon isomerisation of the alkene. Therefore, the Rubottom oxidation was identified as a promising method for the diastereoselective C7-oxidation.



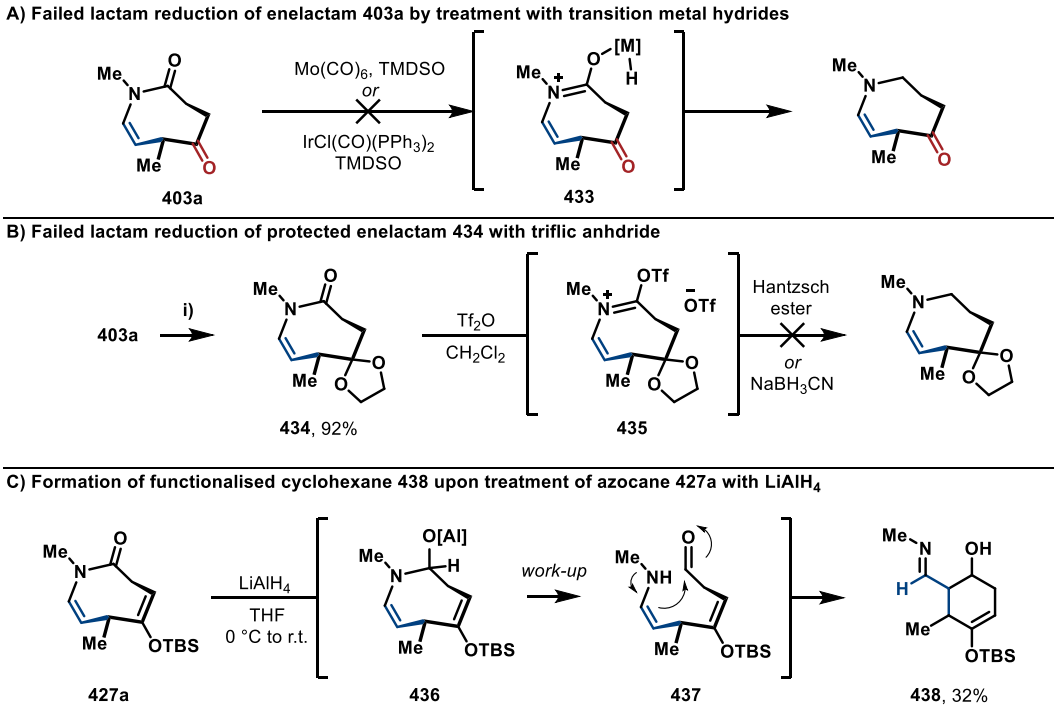
Scheme 95

3.2.2.2 Enelactam reduction

Investigations turned to the lactam reduction, primarily to gain an appreciation for the reactivity of the enelactam functionality of azocanes, but also to test whether a chemoselective lactam reduction in the presence of the ketone was feasible. Additionally, a successful reduction at this stage might provide valuable experience in the handling and purification of azocanes that contain a N-C8 transannular interaction. Chemoselective reduction of lactams (or amides) in the presence of ketones is challenging, but several protocols have been reported,[256] and a few of these have been employed in the synthesis of natural products.[257-259] Among these methodologies, those that employ Lewis-acidic transition-metal hydrides that can selectively coordinate to Lewis-basic amide carbonyl have proved to particularly powerful (see **433**, Scheme 96, A). However, under these conditions the C2-alkene of azocane **403a** might restrict transition-metal hydride reduction of the lactam, by reducing the Lewis-basicity of the lactam carbonyl. In the event, azocane **403a** did not react when subjected to $Mo(CO)_6$/TMDSO[260] or $IrCl(CO)(PPh_3)_2$/TMDSO[261] (Scheme 96A).

Instead, the ketone of azocane **403a** was protected as the 1,3-dioxolane in high yield (92% yield of **434**) to investigate lactam reduction by stronger reducing agents (Scheme 96B). When treated with triflic anhydride, the lactam of protected azocane **434** underwent a clean reaction to form triflimide **435** (as determined by ^{1}H NMR analysis), but subsequent addition of Hantzsch ester[262] or sodium cyanoborohydride[263] resulted in degradation. Finally, silyl enol ether **427a** was treated with lithium aluminium hydride, which resulted in the formation of the unexpected ring contraction product **438** in 32% yield (Scheme 96C). This highly substituted cyclohexane derivative is proposed to form by partial

lactam reduction of silyl enol ether **427a** to form [Al]-intermediate **436**. During work-up **436** likely undergoes ring opening to form acyclic intermediate **437**, the aldehyde and enamide functionalities of which recombine to give cyclohexane **438**. The failure to reduce species **436** might have been due to poor *N*-lone pair overlap with the σ*-orbital of the C-O[Al] bond as a result of the conformation of the azocane ring.



Scheme 96: B) *Reagents and conditions*: i) ethylene glycol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to r.t.

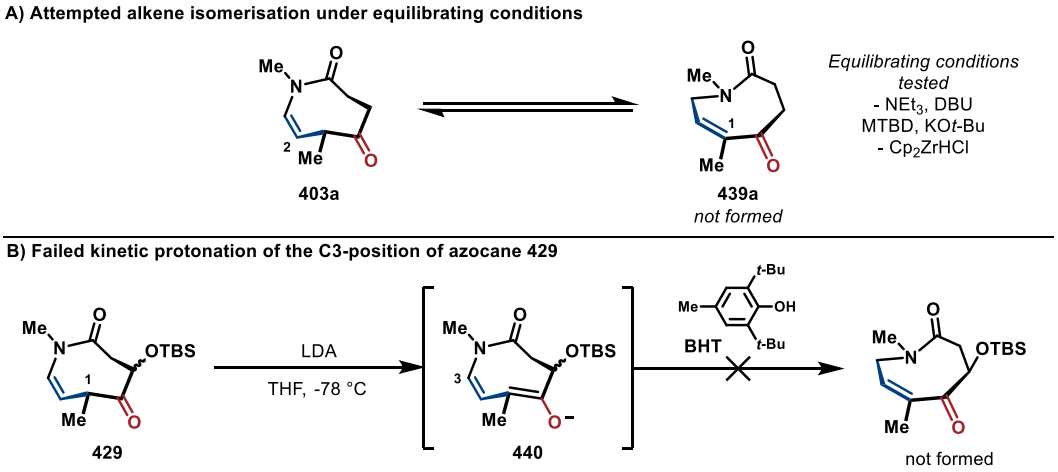
Efforts to reduce the lactam of azocanes containing the enelactam functional group failed under mild chemoselective reducing conditions as well as more forcing conditions. This was believed to be a result of the presence of the C2-alkene, which reduces the nucleophilicity of the lactam carbonyl and promotes ring opening of partially reduced intermediates. As a result of these considerations it was concluded that the lactam reduction should be carried out after alkene isomerisation.

3.2.3 Alkene isomerisation

3.2.3.1 Attempted alkene isomerisation under equilibrating conditions

The next post-cycloaddition transformation to be studied was the alkene isomerisation from the C2-position of azocane formed during the (7+1) carbonylative cycloaddition, to the C1-position as in otonecine. Studies began by subjecting azocane **403a** to various equilibrating conditions in the hope that the C1-alkene isomer was thermodynamically more favourable than the C2-isomer. Azocane **403a** was treated with a range of bases (NEt_3, DBU, MTBD and KO*t*-Bu) but enone **439a** was not observed (Scheme 97A). Similarly, attempts to isomerise the alkene using Schwartz's reagent[264] failed to produce

any of the desired isomer **439a**. Finally, an attempt to protonate the C3-position of enolate **440** (formed by deprotonation of the C1-position of α-siloxyketone **429**) with BHT, a sterically bulky acid, also failed (Scheme 97B). These results indicate that the unwanted C2-alkene isomers (as in azocane **403a**) are thermodynamically more stable than the desired C1-alkene isomers (as in enone **439a**), and so non-equilibrating alkene isomerisation conditions might be required.

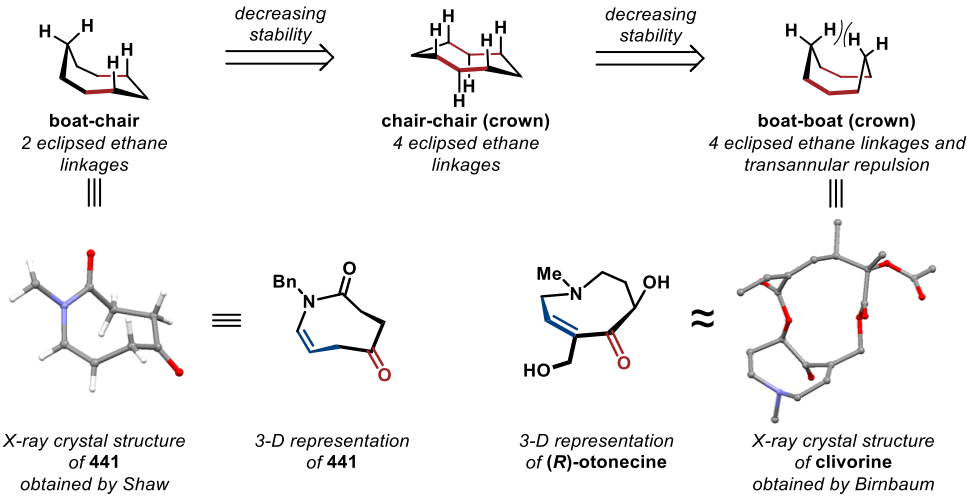


Scheme 97

3.2.3.2 Computational studies into the relative stability of alkene isomers

3.2.3.2.1 Conformations of eight membered rings

Prior to the calculations presented in the following section, it is pertinent to introduce the common conformations adopted by eight membered rings because conformation has a dramatic influence on the stability and reactivity of cyclic molecules.[247] The simplest eight-membered ring, cyclooctane, has been shown to exist predominantly in a boat-chair conformation (Scheme 98).[247] The boat-chair conformation possesses two unfavourable eclipsed ethane linkages (highlighted in red) and no significant transannular repulsions. By comparison, the slightly less stable chair-chair (or crown) conformation contains four eclipsed ethane linkages. Less stable still, the boat-boat conformation exhibits four eclipsed ethane linkages as well as a significant transannular repulsion. It is difficult to predict the conformation of more functionalised eight-membered ring because the addition of functionality might alleviate or introduce unfavourable interactions.[265] Previously, Shaw disclosed a crystal structure of simple azocane **441**.[101] This shows that it adopts a boat-chair conformation in the solid state, which is in accordance with the conformation adopted by cyclooctanone.[266] In contrast, crystal structures of the otonecine-type PAs (including clivorine) show the azocane ring system adopting a boat-boat conformation because of the stabilising N-C8 transannular interaction.[199, 267]



Scheme 98: Common conformations of eight-membered rings and comparison with the conformations adopted by azocane **441** and otonecine.

3.2.3.2.2 Computational studies

The failure to observe the desired C1-alkene isomer **439a** under various equilibrating conditions suggested that there was a large thermodynamic preference for the C2-isomer in azocane **403a**. Further evidence for this proposition was obtained by calculating the relative stability of C2- and C1-alkene isomers using computational methods (*further details are provided in the experimental Section 4.6*). Computational chemistry has proved to be successful in predicting and rationalising the outcomes of reactions, and is therefore increasingly being employed as a predictive tool in the synthesis of natural products.[268-270] Of particular relevance to the proceeding discussion, computational chemistry has been used to predict the outcome of reactions involving thermodynamic equilibria.[271] Therefore, with guidance from Dr. Natalie Fey, low energy conformations of each alkene isomer were identified by carrying out a conformer distribution calculation using the Spartan software. The resulting low energy conformations were optimised by performing energy optimisation calculations using hybrid density functional theory (B3LYP)[272-276] and the 6-31G(d)[277-279] basis set using the Gaussian software.[280] The lowest energy conformation of each alkene isomer, found in this way, were compared to provide an energy difference, which indicated the more thermodynamically stable alkene isomers.

To begin, C2-alkene isomer **403a** and the corresponding C1-alkene isomer **439a**, were compared (Figure 6). The lowest energy conformation of C2-alkene **403a** was identified as boat-chair conformer **BC-403a** where the C1-methyl group is in the equatorial position, which closely resembles the crystal structure of simple azocane **441**, obtained by Shaw (Scheme 98). The second most stable conformation calculated for C2-alkene **403a** was boat-boat conformer **BB-403a**, which was calculated to be 12.7 kJ/mol less stable than **BC-403a**. In contrast, the lowest energy conformation of C1-alkene isomer **439a** was calculated to be boat-boat conformer **BB-439a**, which was slightly preferable to chair-chair conformer **CC-439a** (+0.4 kJ/mol). Notably, the nitrogen lone pair of boat-boat conformer **BB-**

439a is directed towards the σ*-orbital of the C8-ketone, invoking a weak transannular interaction (N-C8 distance of 2.89 Å). Finally, comparison of the most stable conformations of the two alkene isomers (C2-alkene conformer **BC-403a** vs. C1-alkene conformer **BB-439a**) suggests that the C2-alkene isomer is 19.9 kJ/mol more stable than the C1-alkene isomer, which is in line with the findings in Scheme 97. This raised the question: at which point in the proposed total synthesis of otonecine from azocane **403a** will the C1-alkene isomer become more thermodynamically favoured than the C2-isomer? To investigate this question, calculations were carried out to compare C2- and C1-alkene isomers of several possible intermediates towards otonecine.

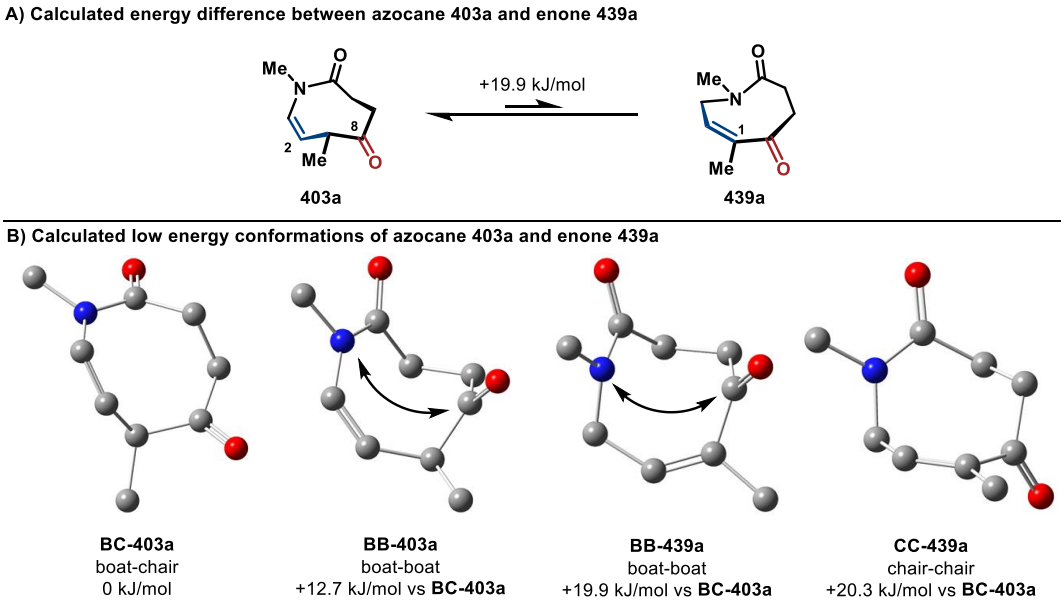


Figure 6

Firstly, lactam reduction products, **442** and **443**, were compared (Figure 7). It was predicted that in the absence of the C5-carbonyl, a N-C8 transannular interaction would be formed, which might increase the stability of the C1-alkene isomer **443** relative to the unwanted C2-isomer. Indeed, C2-isomer **442** was calculated to prefer boat-boat conformation **BB-442** over twisted boat-chair conformer **BC-442** by 3.4 kJ/mol, presumably as a result of a N-C8 transannular interaction (indicated). C1-alkene isomer **443** was predicted to adopt boat-boat conformation **CC-443**, also containing a transannular interaction. Comparison of the favourable conformations of the two alkene isomers, **BB-442** and **CC-443**, revealed a thermodynamic preference for the C2 enamine by +10.5 kJ/mol. Therefore, these results suggest that by reducing the lactam the C1-alkene isomer **443** becomes less disfavoured, but not preferred.

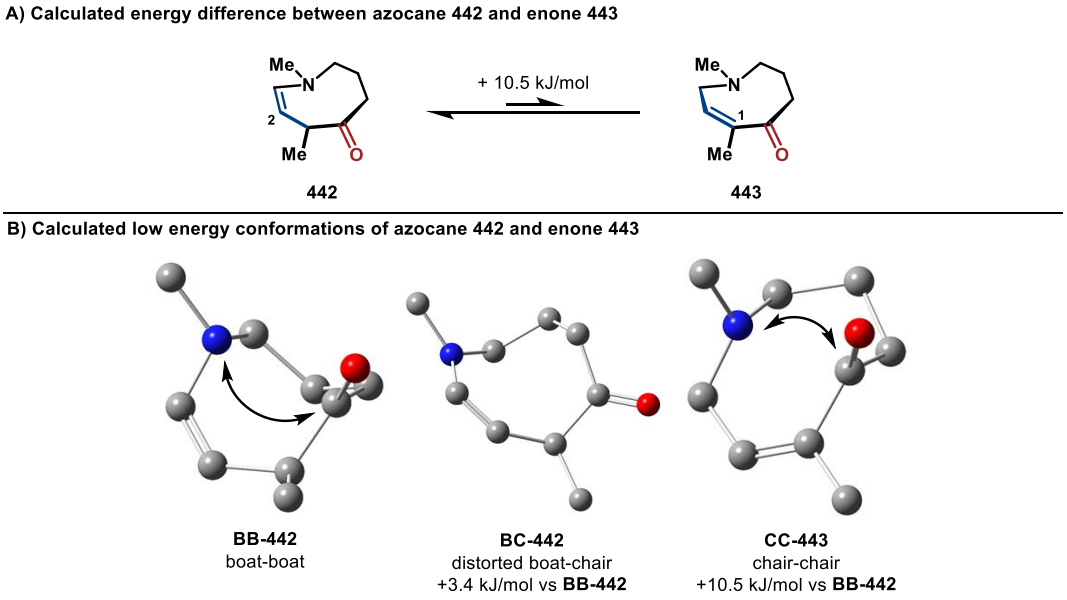


Figure 7

Next, the electronic impact of the C9-alcohol was investigated by comparing alkene isomers, **444** and **445** (Figure 8). C2-alkene **444** was calculated to adopt boat-chair conformer **BC-444** in preference over boat-boat conformer **BB-444** (+9.7 kJ/mol). A hydrogen bonding interaction between the C9-alcohol and C8-ketone (indicated by a dashed line) appears to stabilise the boat-chair conformation. C1-alkene isomer **445** is predicted to adopt boat-boat conformer **BB-445**. Comparison of the favoured conformations of C2- and C1-alkene isomers (**BC-444** vs **BB-445**) showed a strong preference for the undesired C2-alkene isomer (+16.9 kJ/mol), perhaps indicating that the C9-alcohol stabilises the unwanted C2 isomer.

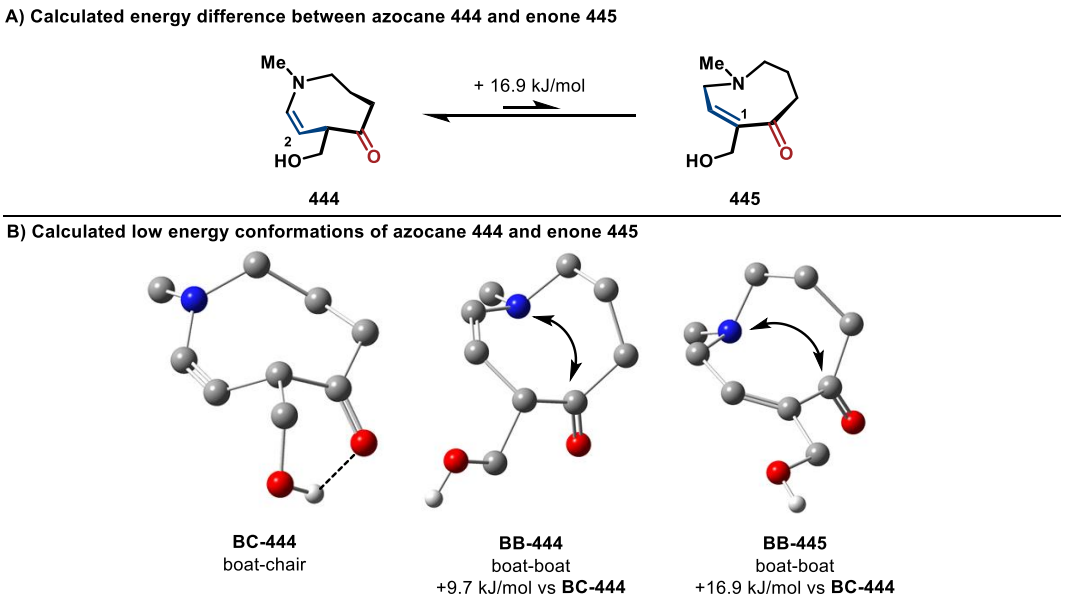


Figure 8

The unexpected thermodynamic preference for the C2-alkene isomer in each of the hypothetical intermediates above prompted comparison of the natural product otonecine with both diastereomers of its C2-alkene isomer, ***trans*-446** and ***cis*-446** (Figure 9). The two lowest energy conformations of ***trans*-446**, chair-chair conformer **CC-*trans*-446** and boat-boat conformer **BB-*trans*-446** were found to be essentially identical in energy (+0.1 kJ/mol). Both conformations contain a C9-alcohol to C8-ketone hydrogen bond while chair-chair conformation **CC-*trans*-446** also contains a transannular C7-OH-N hydrogen bond. The most stable conformation calculated for *cis*-C2-alkene ***cis*-446** was boat-chair conformer **BC-*cis*-446**, which also contained hydrogen bonds between the C8-ketone and each alcohol. Finally, stable conformers of otonecine were calculated, which provided boat-boat conformation **BB-otonecine** as the most stable conformation. Notably, this contains the N-C8 transannular interaction characteristic of the natural product.

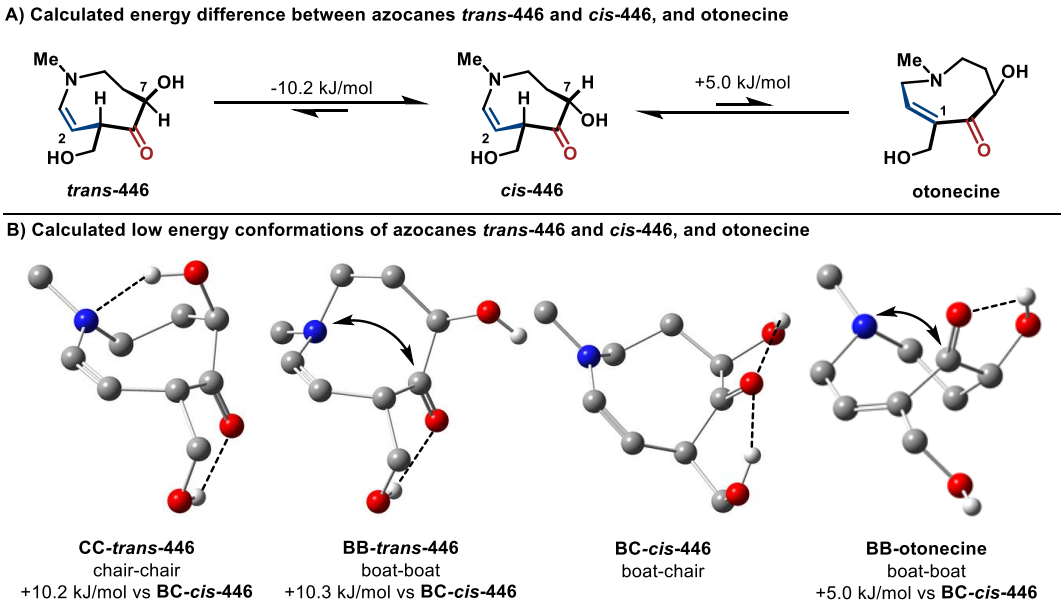
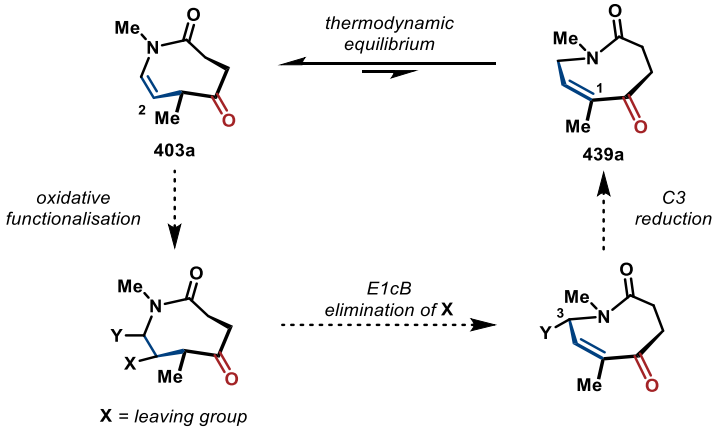


Figure 9

Surprisingly, comparison of the most stable conformations of otonecine and unnatural C2-alkene isomer **446** indicated that the C2-alkene isomer conformation **BC-*cis*-446** was preferred to the otonecine conformer BB-otonecine by +5.0 kJ/mol. This is a small energy difference, which suggests that both alkene isomers might be present in an equilibrating system, although there is no indication in the literature that this is the case. It should also be considered that the results of these calculations might not be accurate. However, the results of the calculations described in this section suggested that the alkene isomerisation step, en route to the total synthesis of otonecine, cannot be achieved under equilibrating condition, so an alternative method was investigated.

3.2.3.3 The development of a kinetic alkene isomerisation

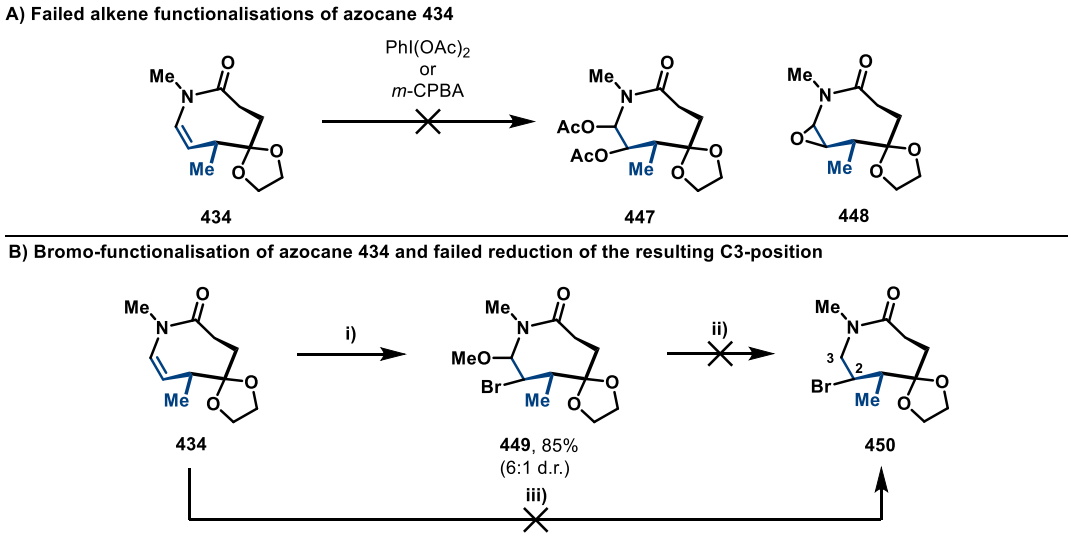
The apparent sustained thermodynamic preference for C2-alkene isomers over the desired C1-alkene isomers necessitated the development of a kinetic alkene isomerisation. It was recognised that this might be achieved by appropriate functionalisation of the enelactam functional group of azocane **403a**. For example, the nucleophilic enelactam moiety might be leveraged to place a leaving group at C2, which might then be elimination by E1cB elimination to reinstall the alkene in the C1-position as in **439a** (Scheme 99). Depending on the conditions used, an additional C3-reduction step might be required in order to render the net-alkene isomerisation, redox neutral.



Scheme 99: Proposed strategy for the kinetic alkene isomerisation.

3.2.3.3.1 Studies in the presence of a protected ketone

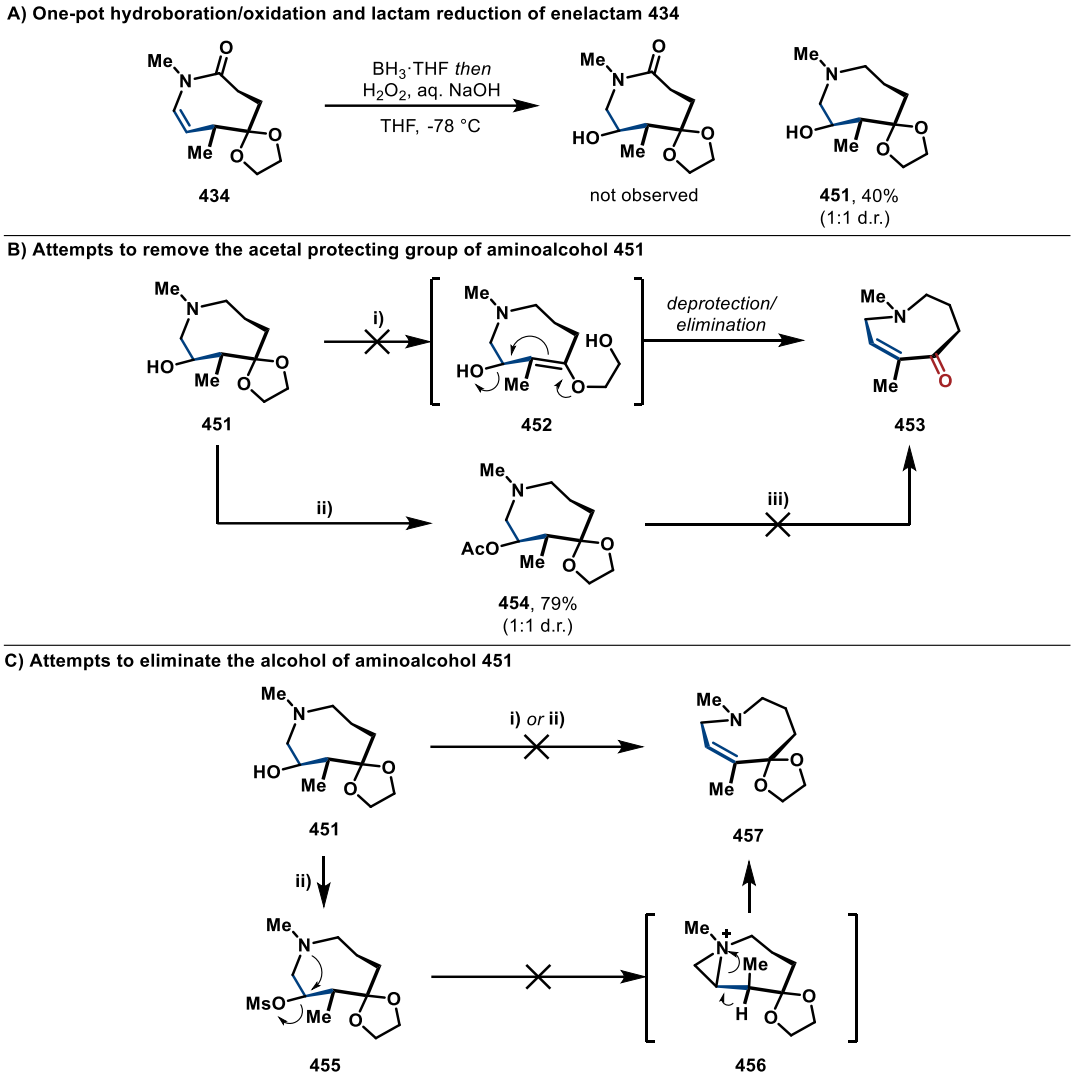
Investigations into the kinetic alkene isomerisation began by subjecting protected azocane **434** to known conditions for the functionalisation of enelactam moieties such that a leaving group is placed at C2. Protected azocane **434** was utilised in the first instance to simplify the system and allow the C3-reduction step to be attempted without the possibility of reducing the ketone. Initially, protected azocane **434** was found to be unreactive in the presence of $PhI(OAc)_2$[281] or *m*-CPBA,[282] precluding the formation of diacetate **447** or epoxide **448** (Scheme 100A). However, on treatment with NBS in methanol,[283] protected azocane **434** reacted to form C3-methoxide **449** in high yield (85%) as an inconsequential mixture of diastereomers (6:1 d.r., *relative stereochemistry not determined*) (Scheme 100B). Subsequent attempts to reduce the C3-position of C3-methoxide **449** by treatment with $BF_3{\cdot}Et_2O/Et_3SiH$ failed to form bromide **450**.[284] Additionally, an attempt to perform a one pot electrophilic bromination/C3-reduction by the combination of NBS with various reducing agents also failed to provide bromide **450**.



Scheme 100: B) *Reagents and conditions*: i) NBS, MeOH, THF, -78 °C to 0 °C to r.t., 1 h; ii) *Failed aminal reduction conditions*: $BF_3{\cdot}Et_2O/Et_3SiH$; iii) *Failed conditions*: NBS/Et_3SiH, $NBS/NaBH_3CN$.

It was envisaged that the problematic C3-reduction step could be avoided by performing an anti-Markovnikov *hydro*functionalisation of protected azocane **434** such that a hydride is introduced at C3. An appealing method of achieving such a transformation is by a hydroboration/oxidation sequence, although this would necessitate the use of a ketone protecting group to avoid overreduction.[285] Accordingly, protected azocane **434** was treated sequentially with $BH_3{\cdot}THF$ and then NaOH/hydrogen peroxide, which provided the lactam reduction product, aminoalcohol **451**, as the sole product in 40% yield (1:1 d.r.) (Scheme 101A). This serendipitous discovery was potentially useful because lactam reduction is one of the post-cycloaddition transformations required in the synthesis of otonecine. Unfortunately, attempts to improve the yield of aminoalcohol **451**, including the use of alternative oxidants (perborate, trimethylamine *N*-oxide[286]), solvents (dichloromethane, toluene) and boranes ($BH_3{\cdot}DMS$, thexyl borane), failed.

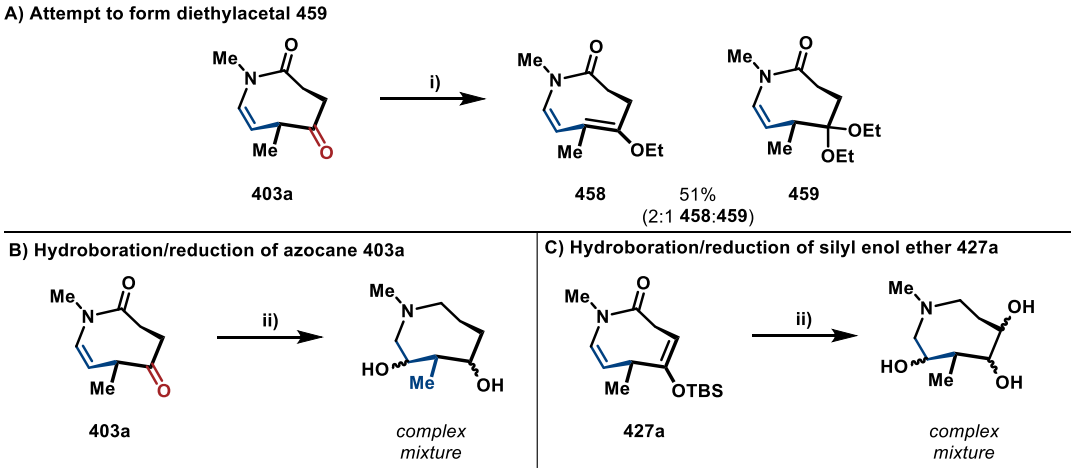
Nevertheless, focus turned to removing the acetal protecting group and eliminating the C2-alcohol of aminoalcohol **451**. Ideally, both transformations would take place in one pot *via* intermediate enol ether **452**, which might eliminate the C2-alcohol under acidic conditions (Scheme 101B). However, several acidic conditions for the deprotection of acetals resulted in the loss of aminoalcohol **451**, but failed to provide deprotected product **453**. Similarly, C2-acetate **454** could not be deprotected under a variety of Brønsted and Lewis-acidic conditions. Finally, attempts were made to eliminate the C2-alcohol prior to removal of the protecting group by treating aminoalcohol **451** with Burgess reagent or methanesulfonyl chloride (Scheme 101C). In the latter case, it was proposed that the mesylate group of **455** would be eliminated by intramolecular S_N2-substitution by the tertiary amine to form aziridinium **456**, which might undergo ring opening to form alkene **457**. However, both conditions failed to provide alkene **457**.



Scheme 101: B) *Reagents and conditions*: i) *Failed conditions*: aq. HCl or HCl, MeOH or pTSA, acetone ii) Ac_2O, DMAP, NEt_3, CH_2Cl_2, r.t., 1 h; iii) Failed conditions: trifluoroacetic acid, CH_2Cl_2 or aq. HCl or $In(OTf)_3$, acetone or $PdCl_2(MeCN)_2$, acetone. C) *Reagents and conditions*: i) Burgess reagent, PhMe; ii) *Conditions attempted*: MsCl, NEt_3, CH_2Cl_2.

Up to this point, difficulties in removing the 1,3-dioxolane protecting group had restricted the use of aminoalcohol **451** in the synthesis of otonecine, and so an alternative C8-ketone protecting group was investigated. To this end, diethylacetal **459** was targeted because acyclic acetal protecting groups are more labile than cyclic acetals (Scheme 102A).[287] When azocane **403a** was treated with triethylorthoformate in the presence of catalytic *p*-TSA, diethylacetal **459** was formed as the minor product along with enol ether **458** in 51% combined yield (2:1, **458**:**459**), which was deemed unsatisfactory for the purpose. Finally, attempts to carry out the hydroboration/oxidation sequence on unprotected azocane **403a** and silyl enol ether **427a**, in the hope that the ketone would not be reduced, provided complex mixtures of products (Scheme 102B and 102C). Despite the potential advantage of the hydroboration/oxidation sequence in terms of step economy, this strategy was abandoned due to

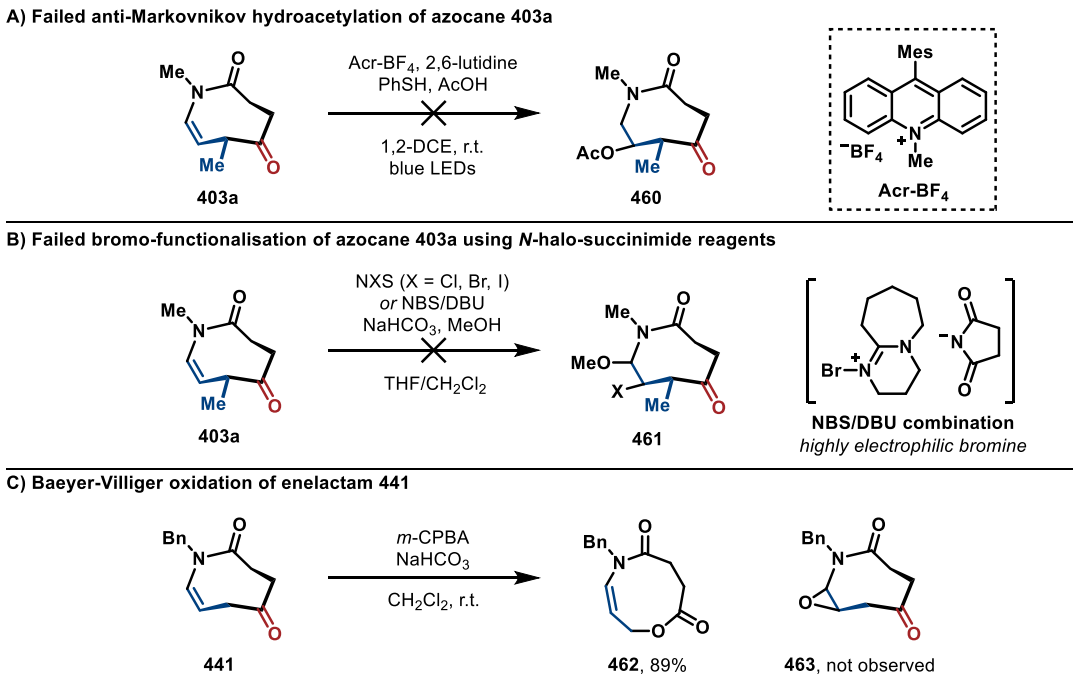
poor yields and the difficulties encountered removing acetal protecting groups. However, the use of BH_3·THF to generate aminoalcohol **451** was the first time that the lactam had been completely reduced, which might benefit future studies.



Scheme 102: *Reagents and conditions*: i) $(EtO)_3CH$, pTSA, EtOH, r.t., 16 h; ii) BH_3·THF, THF, -78 °C to r.t., 1.5 h *then* 30% aq. H_2O_2, 2 M aq. NaOH, 30 min.

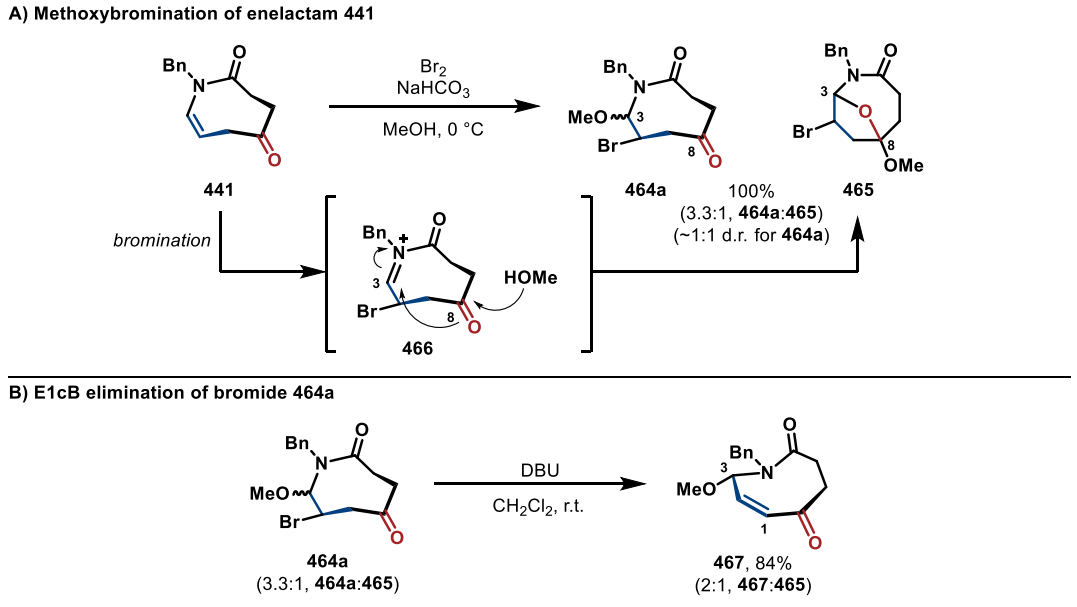
3.2.3.3.2 Studies in the presence of the ketone

*Note: Benzyl-substituted azocane **441** was employed as a model substrate in the following investigations.* It was concluded from the studies in the previous section, that ketal protecting groups should be avoided, so subsequent attempts to functionalise the enelactam moiety employed the unprotected azocanes **403a** and **441**. Recently, Nicewicz and co-workers published a methodology for the anti-Markovnikov hydroacetoxylation of electron-rich alkenes using mild photoredox-catalysed conditions.[288-289] This transformation was promising because it might install an acetate leaving group at the C2-position (see **460**) whilst avoiding the need for an additional C3-reduction step. Unfortunately, azocane **403a** did not react under the hydroacetoxylation conditions, perhaps because the enelactam was too electron-deficient to undergo SET oxidation by the photoredox catalyst (Scheme 103A). Similarly, azocane **403a** did not react to give C3-methoxide **461** when treated with NBS in methanol (Scheme 103B); conditions that were successful in the presence of the 1,3-dioxolane protecting group (see Scheme 100, B). Furthermore, a range of halo-succinimide reagents failed to react with azocane **403a**, including a NBS/DBU combination that provides a highly electrophilic source of bromine.[290] Additionally, attempted epoxidation of azocane **441** to form epoxide **463** with *m*-CPBA failed in place of a high yielding Baeyer-Villiger oxidation providing nine-membered lactone **462** (Scheme 103C). It became apparent from the studies above that azocane **403a** was less reactive towards electrophiles than protected azocane **434**.



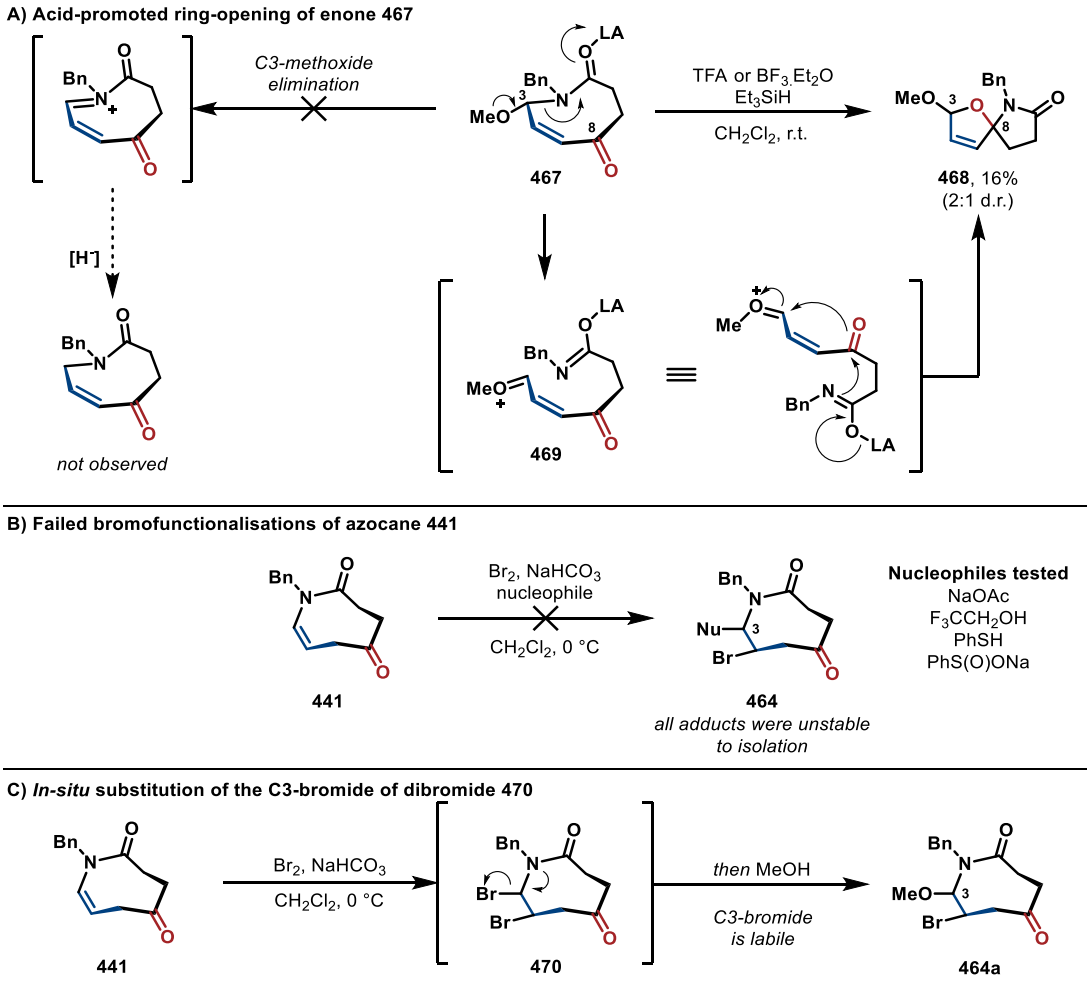
Scheme 103

The enelactam of azocane **441** was eventually found to react with bromine in methanol,[291] which provided C2-methoxide **464a** and bridging acetal **465** as an inseparable mixture (3.3:1 **464a**:**465**) in quantitative combined yield (Scheme 104A). Bridging acetal **465** is proposed to have formed by addition of methanol to the C8-position of iminium **466**, which allows for transannular addition of the C8-oxygen to the C3-iminium. The mixture of C3-methoxide **464a** and hemiaminal **465** was reacted with DBU, which resulted in a rapid and clean E1cB elimination from **464a** to form the C1-alkene **467** as a mixture with acetal **465** (84%, 2:1, **467**:**465**) (Scheme 104B). This result was the first time that the C2-alkene isomer had been isomerised to the desired C1-position.



Scheme 104

To complete the net-alkene isomerisation, the C3-position of enone **467** had to be reduced. Previous attempts to reduce the C3-position of related azocanes failed under acid-promoted conditions (Scheme 100B). Similarly, under both trifluoroacetic acid and $BF_3{\cdot}Et_2O$ promoted conditions in the presence of Et_3SiH reductant, the C3-position of enone **467** was not reduced, but instead spirocycle **468** was isolated (Scheme 105A). Spirocycle **468** is formed as a result of a redox-neutral rearrangement of enone **467**. This rearrangement is proposed to begin with the acid promoted ring-opening of enone **467** by cleavage of the N-C3 bond. The resulting acyclic intermediate **469** then cyclises *via* the C8-ketone. The observed ring-opening of enone **467**, as opposed to elimination of the C3-methoxide, might be promoted by the release of ring-strain and unfavourable orbital overlap between the nitrogen lone pair and C3-O anti-bonding orbitals.



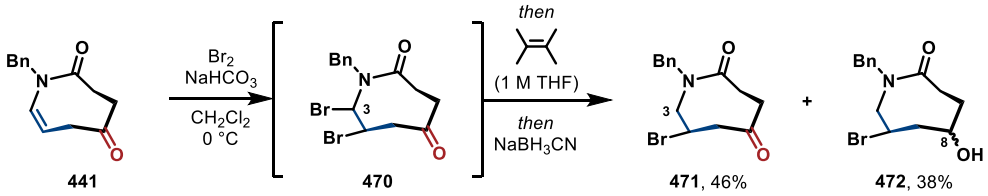
Scheme 105

It was anticipated that the desired C3-reduction of enone **467** might be achieved by replacing the C3-methoxide with a better leaving group. Therefore, azocane **441** was treated with bromine in the presence of a range of alternative nucleophiles, but none of the corresponding adducts **464** were stable enough to be isolated (Scheme 105, B). However, during these studies it was serendipitously discovered that dibromide **470** was stable in a dichloromethane solution and could be cleanly converted to C3-

methoxide **464a** upon addition of methanol, indicating that the C3-bromide of **470** is labile (Scheme 105C). This intriguing observation raised the possibility that the C3-position of dibromide **470** could be reduced by the addition of a suitable reducing agent.

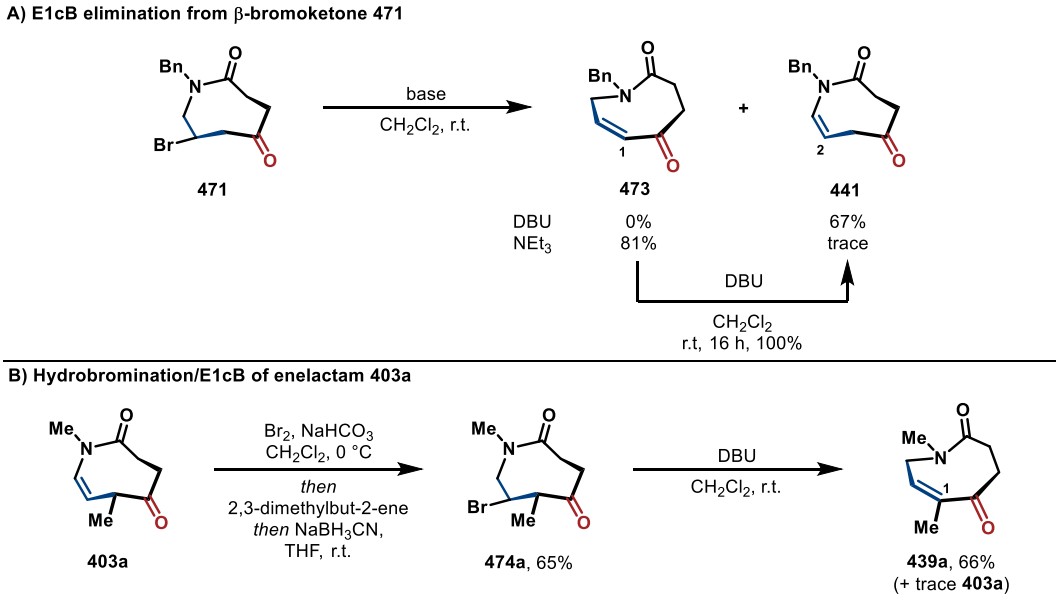
3.2.3.3.3 Identification of a hydrobromination/E1cB sequence

The proposed reduction of the C3-position of dibromide **470** needed to take place in a single pot because **470** degraded during isolation. Therefore, in order to avoid mixing potentially incompatible oxidants (bromine) and reductants (Et_3SiH or $NaBH_3CN$), bromine would be quenched prior to the introduction of the reducing agent. In the event, a solution of azocane **441** and sodium bicarbonate in dichloromethane was treated with bromine until consumption of **441** as determined by a persistent brown colouration (Scheme 106). Next, the alkene, 2,3-dimethylbut-2-ene (as a solution in tetrahydrofuran), was added as a bromine scavenger until the characteristic brown colour of bromine had disappeared. Finally, sodium cyanoborohydride was added to the solution of dibromide **470**, which successfully reduced the C3-position to form bromide **471** in 46% yield along with C8-alcohol **472** in 36% yield. Exploration of the reaction parameters of the newly developed hydrobromination revealed that the incidental addition of tetrahydrofuran during the bromine quench was vital to the success of the reaction because sodium cyanoborohydride is poorly soluble in neat dichloromethane. Additionally, it was discovered that the initial bromination of azocane **441** must be carried out in neat dichloromethane because this failed in the presence of tetrahydrofuran. Furthermore, the mild reducing agent, triethylsilane, failed to reduce the C3-position.



Scheme 106: One-pot hydrobromination of enelactam 441.

Encouraged by the successful development of the hydrobromination conditions, β-bromoketone **471** was subjected to the standard E1cB elimination conditions (DBU in dichloromethane), which proceeded rapidly and cleanly, but formed exclusively the undesired C2-alkene isomer **441** in 67% yield (Scheme 107A). Fortunately, use of a weaker base (NEt_3) allowed a controlled E1cB elimination to give desired C1-alkene isomer **473** in 81% yield. Notably, when C1-alkene isomer **473** was resubjected to basic conditions, the alkene fully isomerised back to the thermodynamically more stable position providing C2-alkene isomer **441** in quantitative yield.



Scheme 107

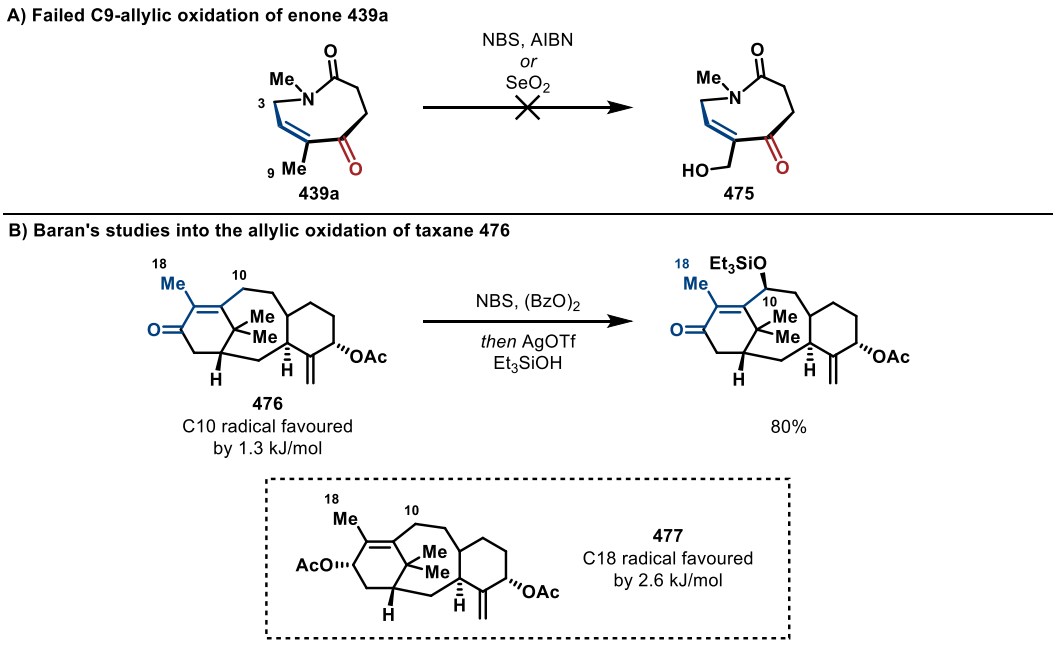
The yield for the two step kinetic alkene isomerisation of model compound **441** (46% then 81% yield) was unsatisfactory due to overreduction of the ketone of bromide **471** during the hydrobromination step. Fortunately, it was discovered that the yield of the hydrobromination improved in the presence of the C1-methyl group of azocane **403a**, providing bromide **474a** in a reproducible 65% yield (Scheme 107B). E1cB elimination from bromide **474a** was slower in the presence of the C1-methyl group, which meant that enone **439a** began to isomerise to form **403a** before bromide **474a** was consumed. Therefore, it was necessary to monitor the E1cB elimination closely by TLC to achieve optimum yields. Future studies should focus on identifying conditions, which avoid this deleterious alkene isomerisation during the E1cB elimination step. The successful development of a kinetic alkene isomerisation was an important milestone in this project, which paved the way for investigations into the remaining post-cycloaddition transformations.

3.2.4 Incorporation of the C9-alcohol

Having developed reliable conditions for the alkene isomerisation step, attention turned to installing the C9-alcohol. It was previously found that 1,2-disubstituted hydroxymethylcyclopropanes were unsuitable substrates for (7+1) carbonylative cycloaddition due to the propensity of the C9-alkoxide of the product azocanes to eliminate under the reaction conditions (Section 3.2.1.1). Therefore, the plan was to install the C9-alcohol by a "late-stage" oxidation after the (7+1) carbonylative cycloaddition. Initially, attempts were made to do so by an allylic oxidation.

3.2.4.1 Allylic C-H oxidation

Unactivated primary C-H bonds are typically the least activated C-H bonds towards oxidation in a given organic molecule, and are therefore very challenging to functionalise.[292-293] By comparison, allylic C-H bonds are more readily oxidised because they are activated by hyperconjugation (π(alkene)-σ*(C-H)) with the adjacent π-system. This consideration prompted attempts to install the C9-alcohol of otonecine by allylic oxidation of enone **439a** (Scheme 108A). One issue with this proposal is the presence of a second allylic position at C3, which may receive additional activation from the lactam nitrogen lone pair. However, competitive oxidation of C3 may be restricted by the increase in ring strain associated with rehybridisation from sp^3 to sp^2 upon homolytic C-H cleavage. Regardless of these concerns, enone **439a** was subjected to two common sets of allylic oxidation conditions, which proceed by differing mechanisms - radical (NBS, AIBN) and pericyclic (SeO_2). Unfortunately, neither sets of conditions provided the desired reactivity when applied to enone **439a**.



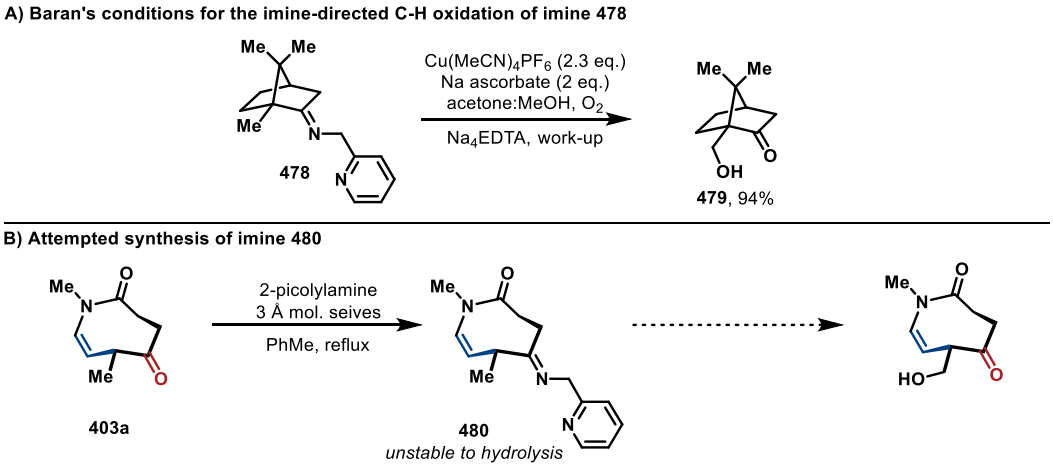
Scheme 108

The difficulty in achieving a selective oxidation of the C9-position in the presence of the competing C3-position is partly explained in Baran and co-workers total synthesis of (-)-taxuyunnanine D.[294] Their synthesis required a regioselective allylic oxidation of the C10 position of taxane **476** in the presence of a second allylic position at C18 (Scheme 108B). The authors carried out DFT calculations to determine the relative stability of intermediate radicals at C10 and C18 in order to predict the preferred site of C-H oxidation. The results suggested that the α,β-unsaturated ketone of taxane **476** directs oxidation to the C10-position instead of the C18-position because the resulting radical at C10 is conjugated. This directing effect could be overcome by carrying out the allylic C-H oxidation on acetate **477** where the C10-position is deactivated. The results presented in Scheme 108A, in combination with

Baran's report, suggest that incorporation of the C9-alcohol by an allylic oxidation is unlikely, so alternative C-H oxidation methods were investigated.

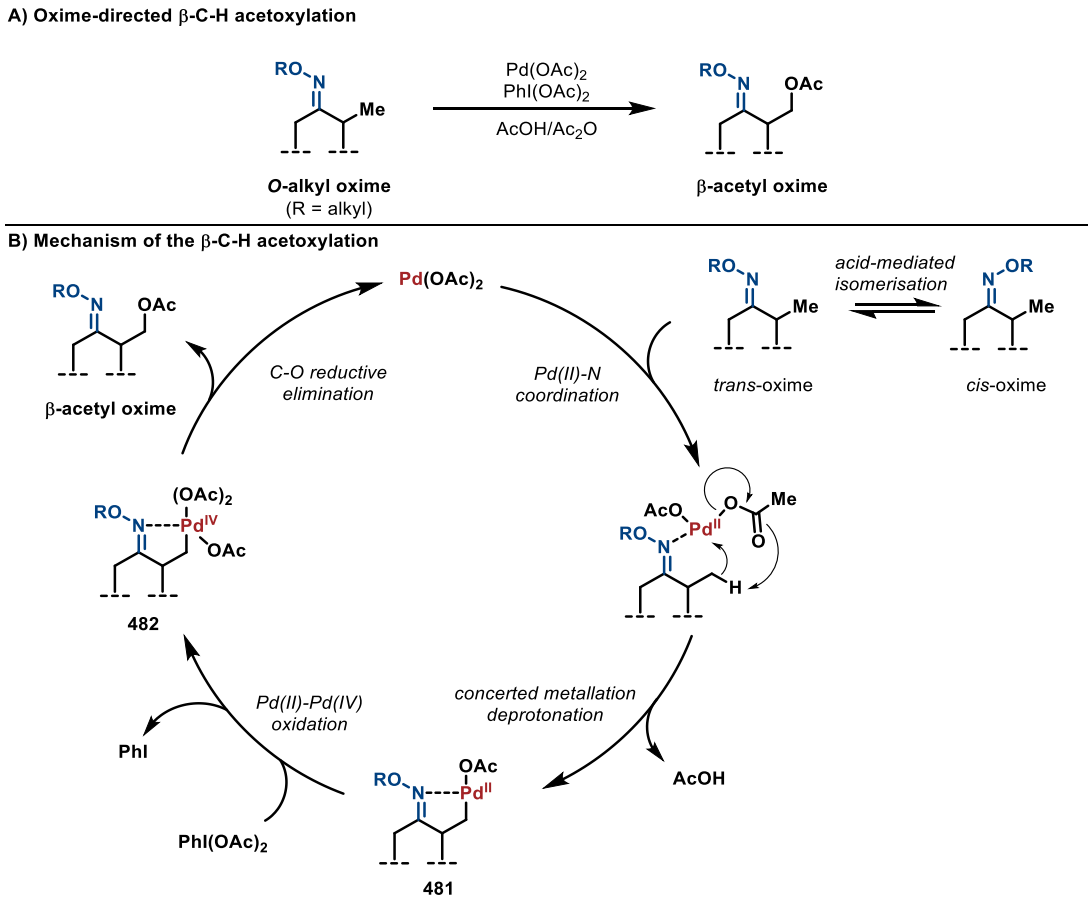
3.2.4.2 Directed C-H oxidation

The use of directing groups to achieve C-H functionalisations can overcome existing electronic preferences in complex molecules.[295] Among these directing group strategies, the β-functionalisation of ketone-derivatives has proved to be very successful. For example, Schönecker and co-workers reported a methodology, which is appealing in the current context, for the copper-catalysed β-oxygenation of imines **478** (Scheme 109A).[296-297] On completion of the β-oxygenation, the imine directing group was removed on work-up to provide β-hydroxy ketones, such as **479**. This methodology was later improved upon by Baran and co-workers.[298-299] Unfortunately, application of this methodology to the β-oxygenation of azocane **403a** failed because imine **480** was highly unstable to hydrolysis, which restricted its isolation and use in the proceeding oxidation (Scheme 109B).



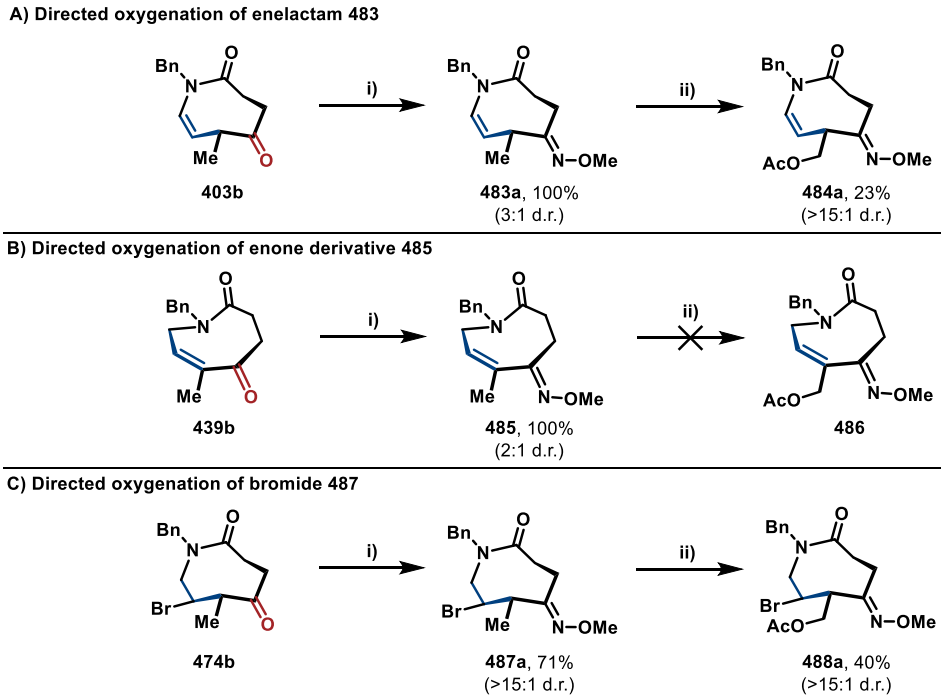
Scheme 109

A similar strategy, originally developed by Baldwin and co-workers,[300] and later Sanford and co-workers, employs ketone-derived oximes as directing groups for β-oxygenation of unactivated C-H bonds (Scheme 110A). In Sanford's catalytic protocol, *O*-alkyl oximes are proposed to coordinate $Pd(OAc)_2$ and direct C-H metallation to the β-C-H bond by a concerted metallation-deprotonation mechanism (Scheme 110B).[301] A stoichiometric oxidant, $PhI(OAc)_2$, oxidises the Pd(II)-centre of intermediate **481** to Pd(IV)-intermediate **482**, which undergoes C-O reductive elimination to provide β-acetyl oximes. These are converted to β-acetoxy ketones upon removal of the oxime. This methodology has been applied in several total syntheses.[302]



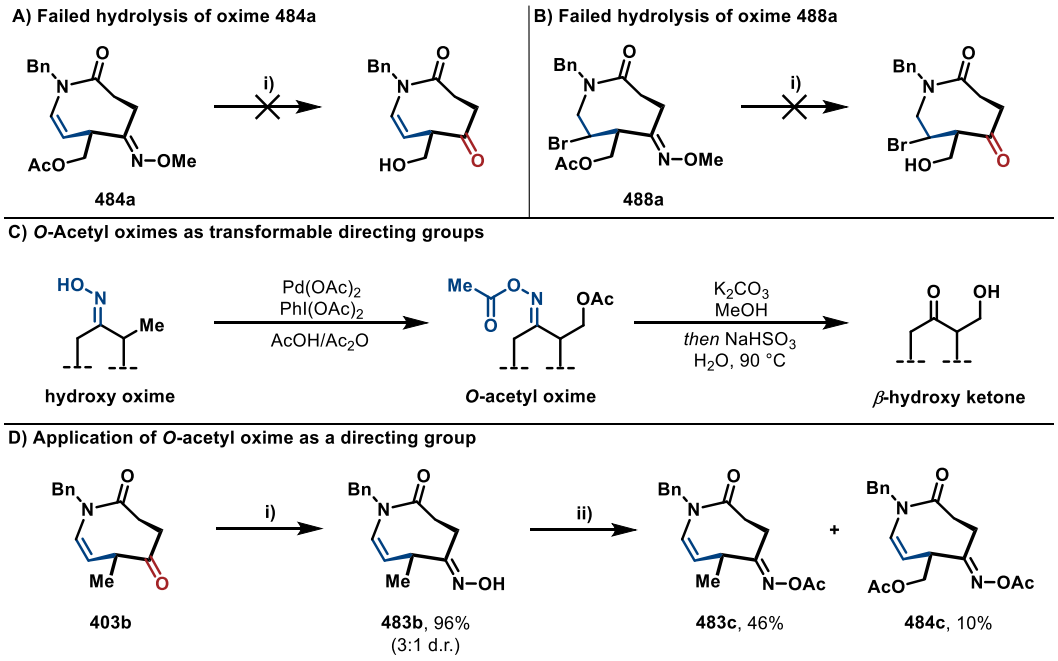
Scheme 110

Efforts to apply this methodology to the total synthesis of otonecine began with the synthesis of *O*-methyl oxime **483a**. This was formed by condensation of methoxyamine hydrochloride onto ketone **403b**, which proceeded in quantitative yield (Scheme 111A). The resulting *O*-methyl oxime **483a** existed as a mixture of diastereomers about the oxime C-N double bond, which interconvert under the acidic reaction conditions. Treatment of *O*-methyl oxime **483a** with $Pd(OAc)_2$ and $PhI(OAc)_2$ in a 1:1 mixture of acetic acid and acetic anhydride formed desired C9-acetate **484a**, albeit in only 29% yield. Next, *O*-methyl oxime **485** was prepared from enone **439b** in quantitative yield to see whether allylic activation of the C9-position would increase the yield of the oxygenation (Scheme 111B). Surprisingly, under oxygenation conditions, allylic C9-acetate **486** was not formed. Fortunately, a modest improvement in yield was achieved when the oxidation was performed on hydrobromination product **487a** (formed in 71% yield from bromide **474b**), which formed acetate **488a** in 40% yield (Scheme 111C).



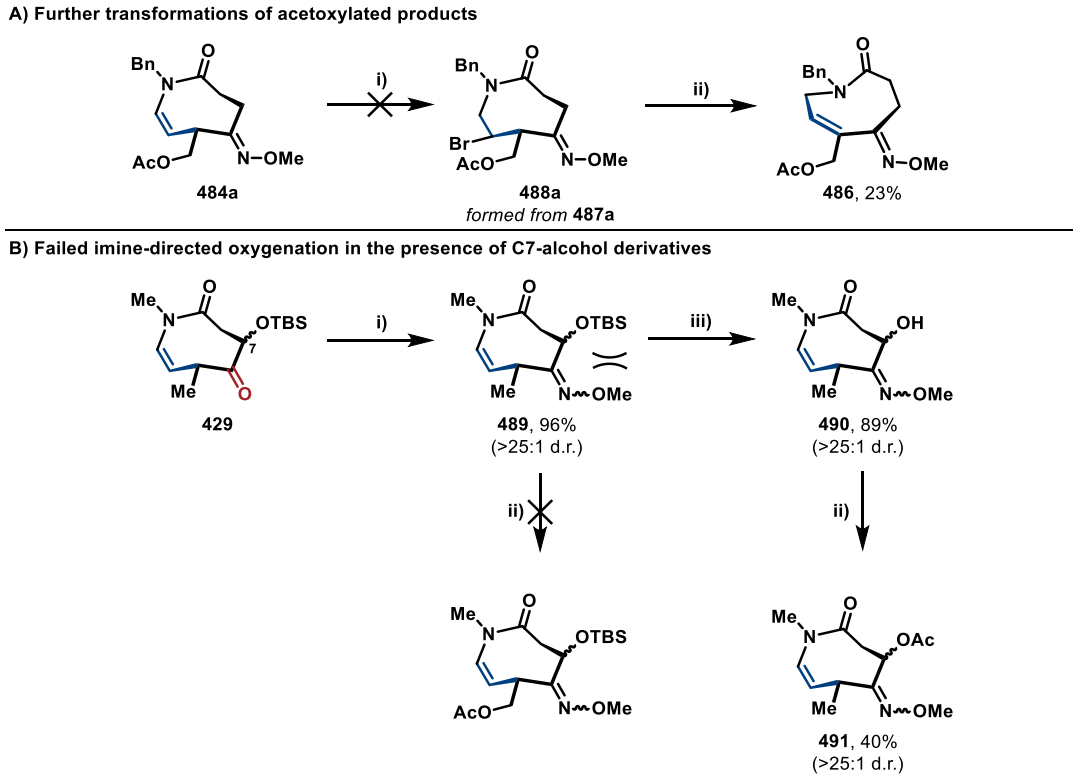
Scheme 111: A + B + C) *Reagents and conditions*: i) $HONH_2 \cdot HCl$, NaOAc, EtOH, r.t., 1 h; ii) $Pd(OAc)_2$, $PhI(OAc)_2$, $AcOH/Ac_2O$, 100 °C, 6 h.

A drawback of using oxime directing groups is they are typically challenging to remove, often requiring harsh acidic conditions. Indeed, all attempts to hydrolyse oximes **484a** and **488a**, under acidic conditions, failed to provide the corresponding ketones, instead resulting in non-specific degradation under more forcing conditions (Scheme 112A and 112B). To circumvent this drawback, Sanford and co-workers reported the use of *O*-acetyl oximes (formed *in-situ* from hydroxy oximes) as removable directing groups for β-oxygenation reactions, which could be removed under comparatively mild conditions when compared to *O*-alkyl oximes (Scheme 112C).[303] However, the electron-withdrawing effect of the acetate group reduces the directing group ability of *O*-acetyl oximes, often resulting in a lower yielding oxygenation when compared to *O*-alkyl oximes. Indeed, when hydroxy oxime **483b**, formed by condensation of hydroxylamine hydrochloride onto azocane **403b** in 96% yield (3:1 d.r.), was subjected to the catalysis conditions, desired oxygenated product **484c** was formed in only 10% yield along with 46% yield of unreacted *O*-acetyl oxime **483c** (Scheme 112D).



Scheme 112: A + B) *Reagents and conditions*: i) $HClO_4$, acetone, r.t., 5 h. D) *Reagents and conditions*: i) $HONH_2{\cdot}HCl$, NaOAc, EtOH, r.t., 1 h; ii) $Pd(OAc)_2$, $PhI(OAc)_2$, $AcOH/Ac_2O$, 100 °C, 6 h.

Undeterred by the difficulties encountered in removing the oxime directing group, further transformations were attempted on C9-oxidised products. Firstly, enelactam **484a** was treated with the recently developed hydrobromination conditions, but bromide **488a** did not form, presumably due to the presence of the electron-rich oxime (Scheme 113A). Nevertheless, E1cB elimination from bromide **488a**, synthesised as in Scheme 111B, resulted in a highly chemoselective elimination of the bromide to form C1-alkene **486** with no trace of C9-acetate elimination side products. The Pd(II)-catalysed C9-oxygenation was also attempted on azocanes bearing a C7-alcohol substituent. Here, the steric bulk of the C7-substituent was expected to have a detrimental effect on the C9-oxygenation by forcing the *O*-alkyl oxime to adopt the unproductive *cis*-geometry (see Scheme 110B). *O*-Alkyl oxime **489**, bearing a C7-TBS-protected alcohol, was formed from azocane **429** under alternative conditions using pyridine as a solvent in excellent yield (96%) and as a single C-N double bond diastereomer (Scheme 113B). As predicted, Pd(II)-catalysed C9-oxygenation of *O*-methyl oxime **489** failed. Therefore, the TBS-protecting group of **489** was removed using TBAF (89% yield) and resulting alcohol **490** was reacted under the catalytic conditions, but no oxidation took place, with C7-acetate **491** being the only product formed. It is clear from these results that the Rubottom oxidation would need to be carried out after the C9-oxygenation and removal of the oxime directing group if this strategy was to employed in the total synthesis of otonecine.



Scheme 113: A) *Reagents and conditions*: i) Br_2, $NaHCO_3$, CH_2Cl_2 *then* 2,3-dimethylbut-2-ene *then* $NaBH_3CN$, THF, 0 °C to r.t., 30 min; ii) DBU, CH_2Cl_2, r.t., 15 min. B) *Reagents and conditions*: i) $MeONH_2$·HCl, pyridine, r.t., 16 h; ii) $Pd(OAc)_2$, $PhI(OAc)_2$, $AcOH/Ac_2O$, 100 °C, 6 h; iii) TBAF, THF, r.t., 30 min.

3.2.4.3 Studies towards improved conditions for oxime-directed C-H acetoxylation

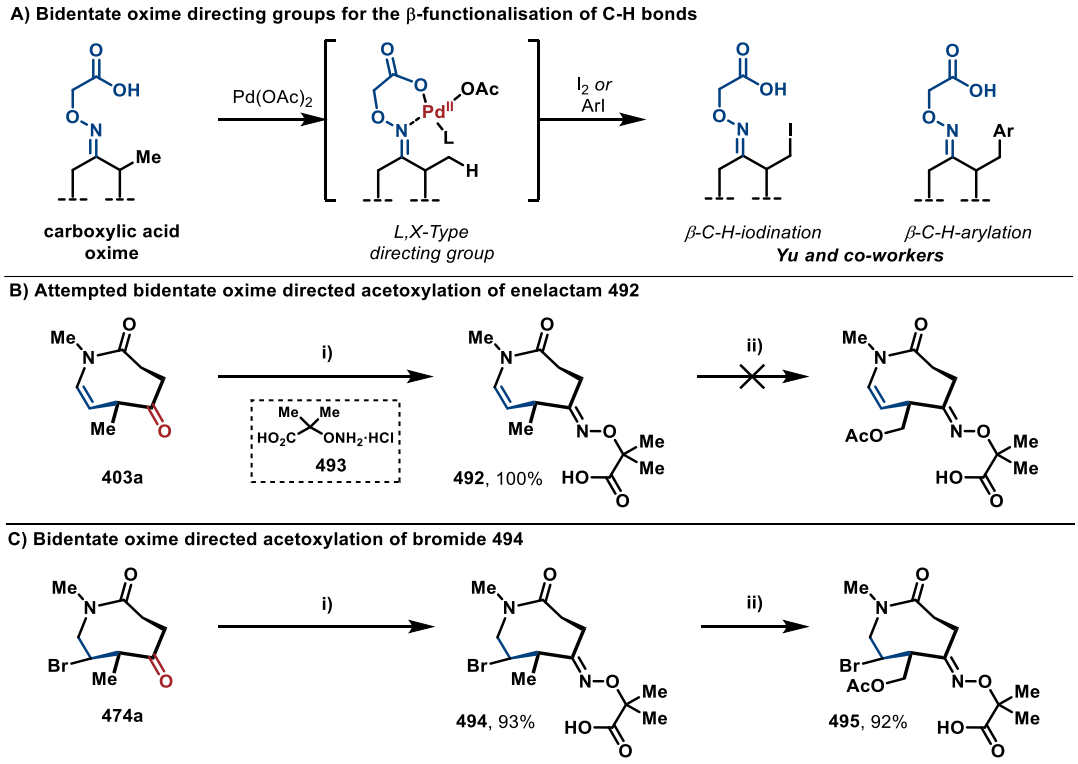
The studies described in the previous section identified several limitations of the oxygenation methodology developed by Sanford and co-workers.[301, 303] For example, *O*-alkyl oxime directing groups exhibited moderate reactivity in the C9-oxygenation of azocanes and these proved problematic to remove. Additionally, the oxygenation is carried out in a 1:1 mixture of acetic acid and acetic anhydride, which drastically limits the functional group tolerance of the process. However, it was recognised that despite its limitations, the β-hydroxylation of oximes achieved a challenging and valuable transformation, which showed promise in the current context. Therefore, attempts were made to improve the methodology.

3.2.4.3.1 Bidentate oxime-based directing groups

Note: *The work in this section was carried out in collaboration with Rachael Ambler, as part of her final year MSci research project at Bristol.*[304]

It was proposed that the low yields obtained in the oxygenation of azocanes in Scheme 111 might be a result of the relatively weak directing ability of mono-dentate oximes, and that this might be overcome by employing a bidentate oxime directing group. Bidentate oxime directing groups have shown large potential in the β-functionalisation of ketone derivatives. For example, the Yu lab have

shown that carboxylic acid oxime directing groups are effective in directing the Pd(II)-catalysed β-arylation and β-iodination of unactivated C-H bonds (Scheme 114A).[305-306] Here, the carboxylic acid oxime acts as L,X-type (L = dative ligand, X = covalent ligand) bidentate directing group for the Pd(II) catalyst, thus promoting C-H metallation and further stabilising the resulting intermediates. Despite the well documented success of bidentate oximes of this type, these have not been reported in Pd(II)-catalysed C-H acetoxylations.



Scheme 114: B + C) *Reagents and conditions*: i) **493**, NaOAc, EtOH, reflux, 1 h; ii) $Pd(OAc)_2$, $PhI(OAc)_2$, $AcOH/Ac_2O$, 80 °C, 6 h;

*Note that from here on, the carboxylic acid oxime directing group shown in azocane **492** will be referred to as **L,X-DG**, where "L,X" refers to the mixed dative/covalent binding mode of the directing group to the Pd(II)-catalyst. This will help to distinguish the directing groups in the following discussion.* To test whether a bidentate directing group could increase the yield of the β-oxygenation of azocane derivatives, L,X-DG azocane **492** was prepared in quantitative yield by condensation of alkoxyamine hydrochloride **493** onto azocane **403a** (Scheme 114B). Directing group L,X-DG, bearing geminal dimethyl substituents, was chosen to aid studies into the removal of this directing group, which will be discussed in Section 3.2.4.3.3. Under identical Pd(II)-catalysed oxygenation conditions, L,X-DG azocane **492** degraded, presumably by acid-mediated hydrolysis of the enelactam functionality. Therefore, alkoxyamine hydrochloride **493** was condensed onto bromide **474a** to provide L,X-DG bromide **494** in 93% yield (Scheme 114C). When subjected to the oxygenation conditions, L,X-DG

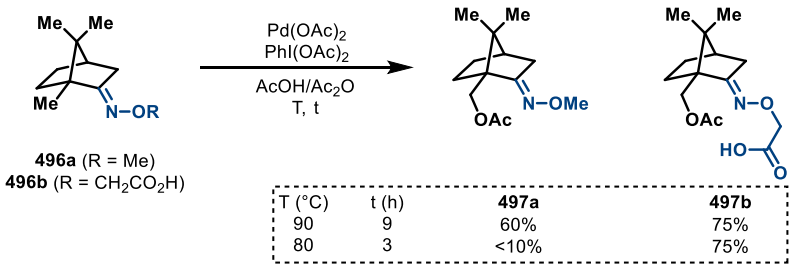
bromide **494** underwent a highly efficient oxygenation, providing C9-acetate **495** in 92% yield. This result demonstrates the beneficial effect of the L,X-type bidentate directing group.

The discovery that L,X-type bidentate directing groups provided a large improvement in the efficiency of the β-oxygenation of azocanes, encouraged further efforts to improve the reaction conditions of the β-oxygenation and oxime removal. Specifically, the following aims were set out:

- Identify an optimal bidentate directing group for the β-oxygenation of C-H bonds.
- Identify an alternative, non-acidic solvent to acetic acid.
- Develop mild conditions for the removal of the new bidentate oxime directing group.

It was recognised that any improvements to the conditions introduced by Sanford and co-workers, would be of interest to the broader synthetic community. Therefore, these studies were carried out using commercially available β-methyl ketones with a view to applying the resulting conditions to the synthesis of otonecine at a later point.

Studies began by confirming that the L,X-type bidentate directing group, identified in the previous section, was indeed superior to monodentate *O*-alkyl oximes. This was achieved by carrying out a direct comparison with an example taken from Sanford's original publication (i.e. *O*-methyl oxime **496a**). Therefore, camphor derivatives, *O*-methyl oxime **496a** and carboxylic acid oxime **496b**, synthesised according to literature procedures, were reacted under the exact β-oxygenations conditions, reported by Sanford (90 °C, 9 hours). Under these conditions, C9-acetate **497a** (R = Me) was formed in 60% yield and C9-acetate **497b** (R = CH_2CO_2H) was formed in 75% yield (Scheme 115). However, when the temperature and duration of the β-oxygenation were decreased (80 °C, 3 hours), the L,X-type bidentate directing group outperformed the monodentate directing group by providing C9-acetate **497b** in 75% yield compared to C9-acetate **497a** in less than 10% yield. It was concluded that the L,X-type bidentate directing group was a superior directing group for the β-oxygenation of C-H bonds.



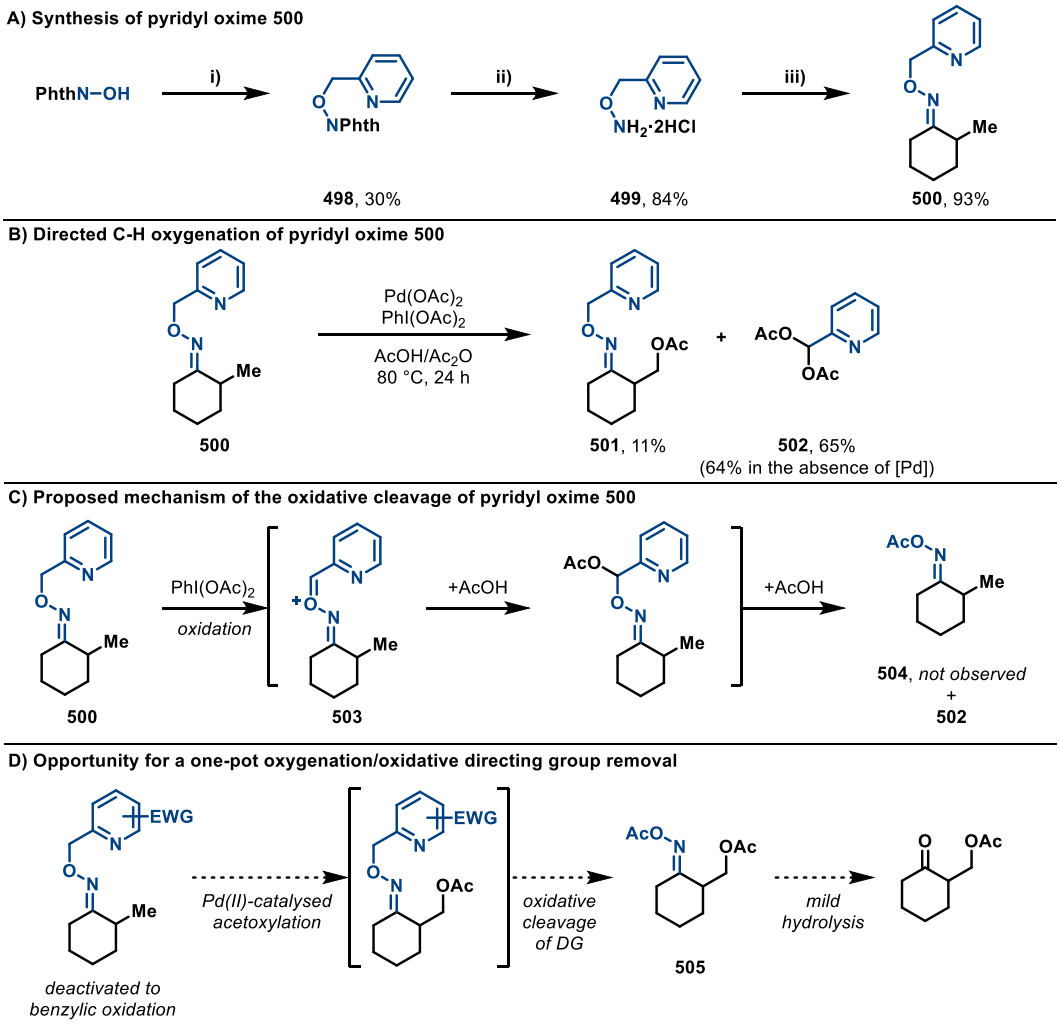
496a (R = Me)
496b (R = CH_2CO_2H)

T (°C)	t (h)	**497a**	**497b**
90	9	60%	75%
80	3	<10%	75%

Scheme 115: Comparison of the C-H oxygenating ability of mono- and bidentate oxime directing groups.

Having confirmed that bidentate directing groups were superior, Ambler investigated alternative bidentate directing groups in the β-oxygenation reaction.[304] A drawback of L,X-type bidentate directing groups was the work-up and purification of compounds containing this directing group was complicated by the carboxylic acid. Therefore, alternative L,L-type bidentate directing group

L,L-DG was designed, where the carboxylic acid was replaced by a datively bonding (L-type) pyridyl group. The studies in this section employed 2-methylcyclohexanone as a simple, commercially available β-oxygenation substrate.



Scheme 116: A) *Reagents and conditions*: i) 2-chloromethylpyridine, NEt_3, MeCN, 80 °C, 2.5 h; ii) conc. HCl, H_2O, 90 °C, 5 h; iii) 2-methylcyclohexanone, NaOAc, EtOH, 80 °C, 16 h.

Alkoxyamine dihydrochloride **499** was synthesised by Ambler in two steps (Scheme 116A). *N*-Hydroxyphthalimide was alkylated with 2-chloromethylpyridine to provide *N*-alkoxyphthalimide **498** in 30% yield, which was subsequently hydrolysed to give the alkoxyamine dihydrochloride **499** in 84% yield. This was condensed onto 2-methylcyclohexanone to give L,L-DG substrate **500** in 93% yield. Under the β-oxygenation conditions, L,L-DG substrate **500** provided desired acetate **501** in 11% yield along with 65% yield of diacetate **502** (Scheme 116B). A control experiment, carried out in the absence of $Pd(OAc)_2$ under otherwise identical conditions, resulted in the formation of diacetate **502** in nearly identical yield (64% yield), which indicated that $PhI(OAc)_2$ was the oxidant in this process. Based on this evidence, it was proposed that diacetate **502** was formed by $PhI(OAc)_2$-mediated oxidation of the activated benzylic position of L,L-DG substrate **500**, to give conjugated species **503**, which is cleaved

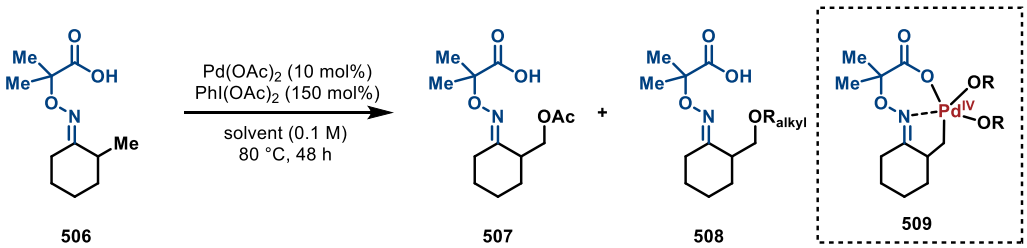
by two equivalents of acetic acid (Scheme 116C). This mechanism suggests that *O*-acetyl oxime **504** should be formed as a side-product, although this was not observed.

This unanticipated oxidative degradation of L,L-DG substrate **500** raised an interesting possibility in terms of directing group removal (Scheme 116D). It was proposed that by deactivating the benzylic position of the L,L-type directing group towards oxidation, β-oxygenation might become the faster process. This might allow the development of a one-pot β-oxygenation/oxidative degradation process to provide β-acetyl oximes **505**, which can be converted to the corresponding ketones under relatively mild conditions. This intriguing proposal has not been investigated further at this point.

3.2.4.3.2 Solvent screen

Sanford's reported conditions for the β-oxygenation of oximes uses acetic acid as a solvent, which drastically limits the scope of the reaction.[301] A milder alternative would be beneficial both for the total synthesis of otonecine and for the wider synthetic community. It was hoped that the improved activity of L,X-DG would allow an alternative solvent to be employed. A potential disadvantage of moving away from acetic acid as a solvent, was that this might restrict isomerisation of the oxime C-N double bond, which would limit the yield of the β-oxygenation.

The results of a solvent screen are shown in Table 14. Cyclohexanone-derivative **506**, bearing L,X-DG (prepared in one step from 2-methylcyclohexanone), was subjected to Pd(II)-catalysis with $PhI(OAc)_2$ in a 1:1 mixture of acetic acid, which formed acetate **507** was formed in 76% yield (Entry 1). Neat acetic anhydride provided a clean reaction and high yield of acetate **507** (71%, Entry 2), but acetic anhydride contains acetic acid, so was avoided. The non-polar and polar-aprotic solvents indicated in Entry 3, resulted in significant degradation and poor yields of acetate **507** (10–31% yield, Entry 3). Interestingly, methanol provided methyl ether **508a** (R_{alkyl} = Me) in 75% yield with less than 5% of acetate **507** formed (Entry 4). Using a very similar $Pd(OAc)_2/PhI(OAc)_2$/MeOH system, Chen and co-workers developed a protocol for the directed synthesis of alkyl ethers by C-H functionalisation.[307-308] They proposed that the formation of occurs *via* reductive elimination from an intermediate analogous to Pd(IV)-alkoxide intermediate **509**.[308] Despite the excellent yield of the β-methoxylation in methanol, these products were not appealing in the context of the total synthesis of otonecine because methyl ethers require harsh conditions to be converted to the corresponding alcohols. Therefore, the β-oxygenation was carried out in sterically demanding alcohol solvents in order to dissuade $C\text{-}O_{alkyl}$ reductive elimination and favour formation of acetate **507**. Trimethylsilanol and isopropanol failed to provide acetate **507**, but *t*-butanol formed **507** in 29% yield along with 10% of corresponding *tert*-butyl ether **508b** (R_{alkyl} = *t*-Bu) (Entry 5). Finally, addition of toluene as a co-solvent with *t*-butanol (1:1 ratio) provided a modest improvement in the yield of acetate **507** (34%, Entry 6).



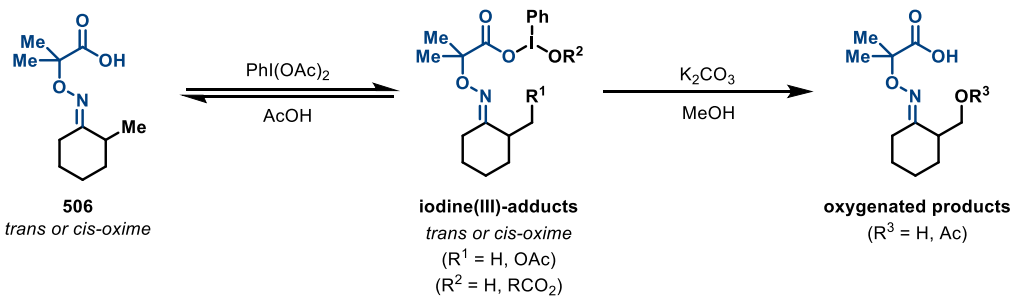
506 507 508 509

Entry	Solvent	Yield of 507[a]	Yield of 508[a]
1	$AcOH/Ac_2O$ (1:1)	76%	-
2	Ac_2O	71%	-
3	cyclohexane, 1,2-DCE, 1,4-dioxane, PhMe, MeCN, EtOAc	10-31%	-
4	MeOH	<5%	75%
5	*t*-BuOH	29%	10%
6	***t*-BuOH/PhMe (1:1)**	**34%**	**30%**

[a] *In-situ* NMR yield measured against an internal standard.

Table 14: Selected results from a solvent screen for the β-oxygenation of bidentate oxime **506**.

During the studies detailed above, it was noticed that a significant number of side-products were being formed by acetate exchange with the $PhI(OAc)_2$ oxidant (Scheme 117). This resulted in the formation of complex mixtures of iodine(III)-adducts, which impeded the desired oxygenation reaction and complicated analysis of the reaction mixtures. Presumably by carrying out the reaction in acetic acid, the formation of such iodine species is statistically disfavoured. After some experimentation it was found that the unwanted iodine(III)-adducts could be broken up at the end of the reaction by stirring the crude mixture with potassium carbonate in methanol. This unanticipated reactivity might be avoided by choosing an alternative oxidant, such as oxone, which has been shown to be able to oxidise Pd(II) to Pd(IV) in related transformations.[309] Despite the efforts above, a suitable replacement for acetic acid was not identified. With the exception of methanol (Entry 4), all of the solvents tested resulted in the formation of multiple unidentifiable side-products, which resulted in poor yields of acetate **507** and hard to purify crude mixtures.



506
trans or cis-oxime

iodine(III)-adducts
trans or cis-oxime
(R^1 = H, OAc)
(R^2 = H, RCO_2)

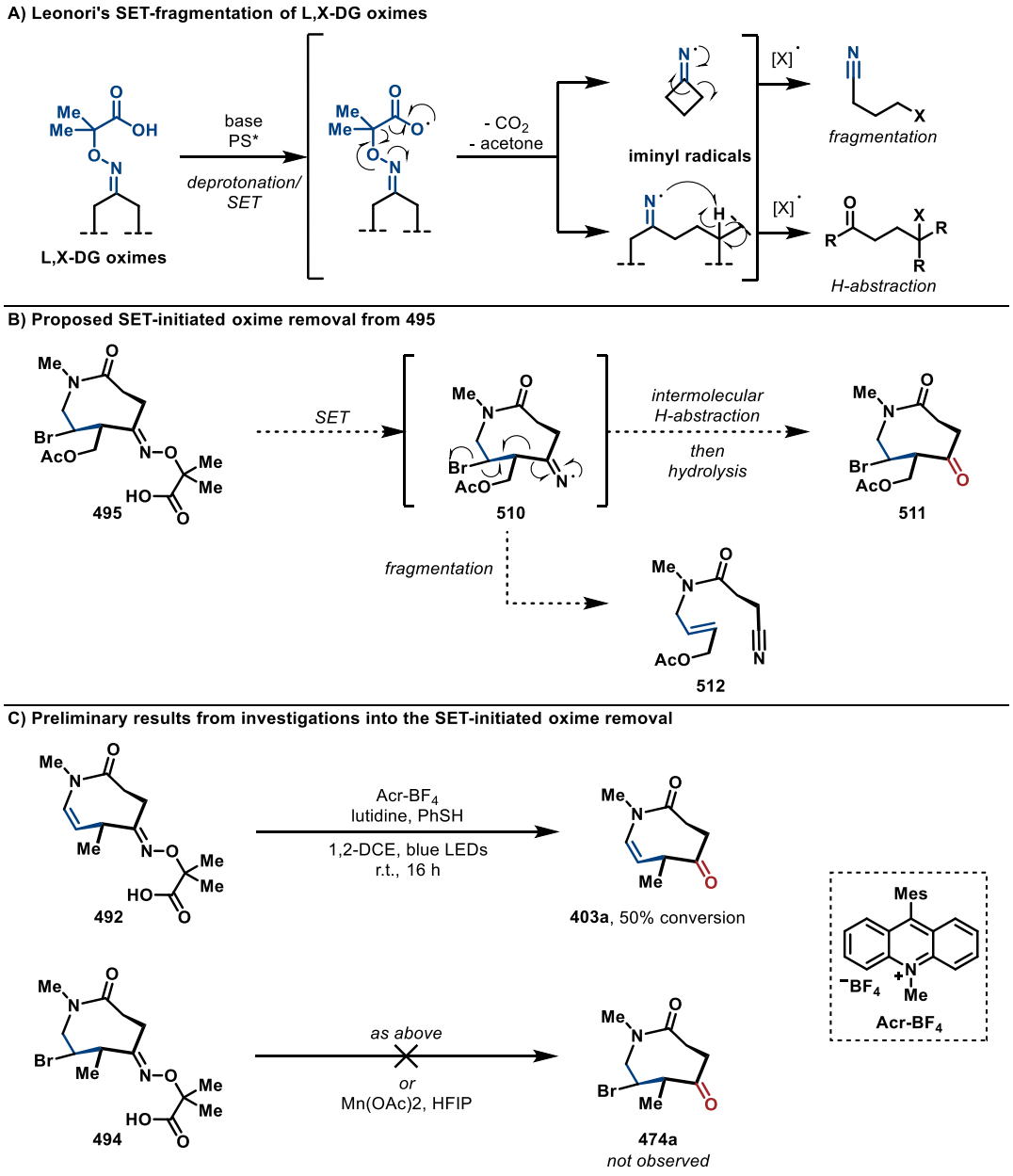
oxygenated products
(R^3 = H, Ac)

Scheme 117: Iodine(III)-adducts formed between carboxylic acid directing groups and $PhI(OAc)_2$.

3.2.4.3.3 Removal of the bidentate oxime directing group

It was previously discussed that oximes are difficult to remove and often require very harsh acidic conditions to do so, which restricts their use as directing groups (Scheme 112).[303] Therefore, the success of β-oxygenation methodology in the synthesis of otonecine hinged on identifying a suitable means of removing the L,X-type oxime directing group. The *gem*-dimethyl substituted directing group L,X-DG was chosen because it has been shown to undergo fragmentation by single electron transfer (SET).[310] For example, Leonori and co-workers have shown that identical L,X-DG oximes can undergo a SET initiated fragmentation when subjected to photoredox catalysis, resulting in the formation of iminyl radicals (Scheme 118A).[311] The iminyl radicals proceeded to undergo further fragmentation, or intramolecular hydrogen abstraction to generate various valuable products. It was proposed that SET degradation of L,X-DG might be leveraged as a method of removing the directing group. For example, photoredox-initiated SET degradation of L,X-DG acetate **495** would form iminyl radical **510**, which might be trapped by *intermolecular* hydrogen abstraction and imine hydrolysis to form ketone **511** (Scheme 118B). One concern with this proposal was iminyl radical **510** might alternatively undergo further fragmentation and elimination of the β-bromine atom to form linear nitrile **512**. Yu and co-workers have reported that related L,X-DG directing groups can be removed by $Mn(OAc)_2$-initiated SET fragmentation, although this requires expensive hexafluoroisopropanol as a solvent.[312]

Preliminary studies were carried out on L,X-DG azocane **492** because of the ease of preparation of this molecule and because it wasn't expected to undergo ring-opening fragmentation (Scheme 118C). Based on Leonori's research and prior experience with Nicewicz conditions for the hydroacetylation of alkenes, highly oxidising acridinium photocatalyst **Acr-BF$_4$** ($^*E_{1/2}$ = 2.2 V vs SCE)[288] was employed along with lutidine as a base, and thiophenol as a hydrogen-donor, in 1,2-dichloroethane. Under these conditions, L,X-DG azocane **492** was irradiated with blue LED's (*Further details are available in Experimental Section 4.4*), which resulted in a remarkably clean reaction achieving 50% conversion (as determined by ^{1}H NMR analysis of the crude reaction mixture) to the desired azocane **403a** over 16 hours. However, when L,X-DG bromide **494** was subjected to identical conditions, no reaction was observed. Similarly, L,X-DG bromide **494** did not react under Yu's conditions for the removal of oximes ($Mn(OAc)_2$/hexafluoroisopropanol). Clearly, the photoredox-initiated SET cleavage of L,X-DG shows great promise for achieving a mild method of removing the directing group, but further optimisation of the reaction conditions is required.

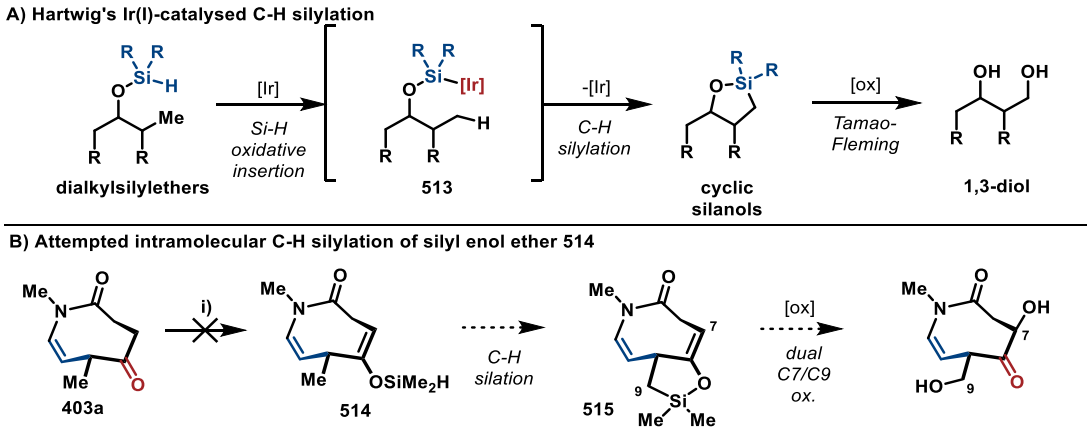


Scheme 118

The oxime-directed C-H oxygenation methodology developed by Sanford showed promise as a method to install the C9-alcohol of otonecine. However, in order to realise this potential, several improvements to the original conditions are required. In collaboration with Ambler, a superior bidentate oxime directing group, L,X-DG, was identified, which provided a significant yield increase under less forcing conditions. Unfortunately, an alternative reaction solvent to acetic acid was not identified. Finally, preliminary studies indicate that photoredox-initiated SET cleavage could serve as a mild method for the removal of L,X-DG. Further optimisation may ultimately provide a valuable methodology both for the synthesis of otonecine, but also for the wider synthetic community.

3.2.4.4 Tamao-Fleming strategy for the installation of the C9-alcohol

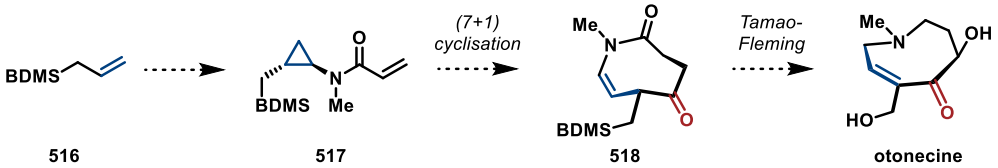
During the studies into directed C-H oxygenations, interest arose in the Ir(I)-catalysed β-C-H oxygenation of silanols, developed by Hartwig and co-workers.[313] The mechanism of this transformation is proposed to begin with the formation of Ir(I)-intermediate **513** by Ir(I)-metallation of the Si-H bond of dialkylsilylethers (Scheme 119A). Intramolecular metallation of the β-C-H bond of Ir(I)-intermediate **513** is followed by C-Si reductive elimination to form cyclic silanols. Therefore, the dialkylsilylether moiety acts as a covalent directing group for Ir(I)-catalysed C-H silylation of the β-C-H bond. Tamao-Fleming oxidation of cyclic silanols affords 1,3-diols as a product of net-β-C-H oxygenation of dialkylsilylethers. This methodology has been applied in a complex natural product setting.[314] In what would be a novel application of the methodology, it was proposed that a silyl enol ether such as **514** might be a suitable substrate for Ir(I)-catalysed β-C-H silylation, forming silacycle **515** (Scheme 119B). Dual Tamao-Fleming/Rubottom oxidation of which might install both the C9 and C7 alcohols in a single pot. Brief attempts to form silyl enol ether **514** were met with difficulty due to silyl enol ether hydrolysis, which precluded investigations into the C-H silylation step. Future attempts should focus on a more stable silyl enol ether, bearing larger alkyl groups.



Scheme 119: A) *Reagents and conditions*: i) LDA, $ClSiMe_2H$, DMPU, THF, -78 °C, 30 min; ii) $[Ir(OMe)(cod)]_2$, 3,4,7,8-tetramethyl-1,10-phenanthroline, norbornadiene, THF, 120 °C.

The investigations above inspired a potential solution to the challenge of introducing the C9-alcohol of otonecine. This involved the use of a C9-silane as a masked alcohol, which could be incorporated at an early point in the synthesis and unmasked by Tamao-Fleming oxidation at a later time. Silanes have been used extensively as masked alcohols in complex settings.[315-317] Of the various silanes that have been shown to undergo Tamao-Fleming oxidation, dimethylphenylsilanes have received the most attention because they are particularly stable to a broad variety of commonly encountered conditions. However, the highly acidic conditions required to activate dimethylphenylsilanes for Tamao-Fleming oxidation (e.g. $HBF_4 \cdot Et_2O$), were undesirable in the current synthesis because several azocane intermediates have been found to be unstable under acidic conditions.

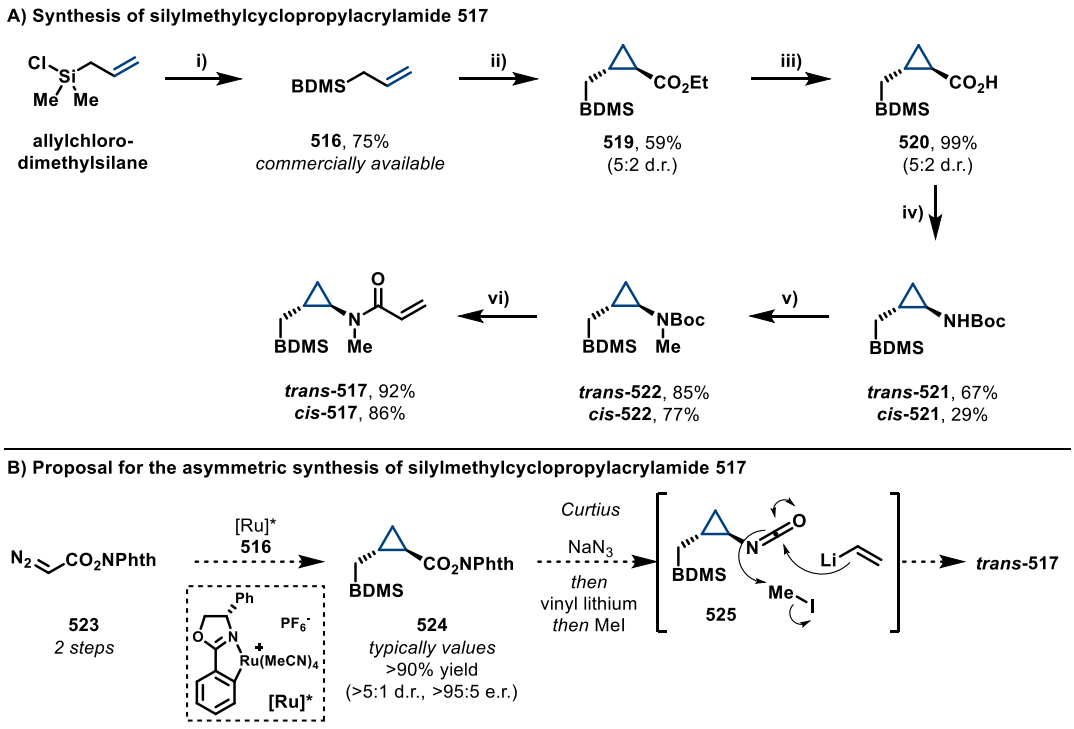
Therefore, investigations into the Tamao-Fleming approach employed the benzyldimethylsilane (BDMS) group, which can be activated by reaction with TBAF.[318] To implement this strategy, the BDMS group was incorporated at the beginning of the synthesis *via* allyl silane **516** (Scheme 120). Allyl silane **516** would be advanced to 1,2-disubstituted silylmethylcyclopropane substrate **517**, which would provide azocane **518** upon (7+1) carbonylative cycloaddition. Silylmethylcyclopropanes had not been investigated in rhodacyclopentanone based methodologies, developed at Bristol, so it was unclear if **517** would be a suitable substrate for (7+1) carbonylative cycloaddition. At the outset, it was unclear at which point the Tamao-Fleming oxidation would take place in the synthetic sequence, so this would be determined at a later stage.



Scheme 120: Proposed Tamao-Fleming strategy for the introduction of the C9-alcohol.

3.2.4.5.1 Synthesis of silylmethyl-substituted cyclopropanes

Investigations into the Tamao-Fleming approach for the installation of the C9-alcohol of otonecine began with the synthesis of 1,2-disubstituted silylmethylcyclopropane **517** (Scheme 121A). The synthesis began with allylbenzyldimethylsilane **516**, which was commercially available, but was also synthesised by reaction of benzylmagnesium chloride with allyl(chloro)dimethylsilane in 75% yield on a 100 mmol scale. Rh(II)-catalysed cyclopropanation with ethyl diazoacetate proceeded to give ester **519** in 59% yield and 5:2 d.r.. Ester hydrolysis (99% yield, 5:2 d.r.) and Curtius rearrangement proceeded in excellent yields, and the resulting diastereomeric cyclopropylamines, ***trans*-521** (67% yield) and ***cis*-521** (29% yield), were separated by column chromatography. Both diastereomers of cyclopropylacrylamide **517** are likely productive in the (7+1) carbonylative cycloaddition, so both diastereomers of protected amine **521** were carried through the *N*-methylation and acrylate formation steps in excellent yield. This robust synthesis produced multi-mmol quantities of cyclopropylacrylamide **517**, which enabled investigations into the (7+1) carbonylative cycloaddition and post-cycloaddition steps.



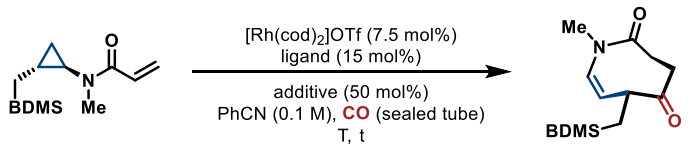
Scheme 121: A) *Reagents and conditions*: i) BnCl, Mg, Et_2O, reflux, 16 h; ii) $Rh_2(OAc)_4$, ethyl diazoacetate, CH_2Cl_2, r.t., 16 h; iii) 4 M aq. NaOH, MeOH, 50 °C, 2 h; iv) diphenylphosphoryl azide, NEt_3, *t*-BuOH, 80 °C, 72 h; v) NaH, MeI, THF, 50 °C, 5 h; vi) trifluoroacetic acid, CH_2Cl_2, r.t., 30 min *then* acryloyl chloride, K_2CO_3, acetone-water, 0 °C to r.t., 16 h.

In the future, it might be necessary to synthesise cyclopropylacrylamide **517** in an enantioenriched form for the asymmetric synthesis of (*R*)-otonecine. This might be achieved by a methodology published by Mendoza and co-workers for the Ru(II)-catalysed asymmetric cyclopropanation of alkenes (including allylsilanes) to give *trans*-1,2-disubstituted cyclopropyl esters **524** (Scheme 121B).[319] The synthetic versatility of the resulting phthalimide cyclopropyl esters **524** was demonstrated through various transformation including a Curtius rearrangement. Inspired by Mendoza's methodology and a report by Zhang and Qian,[320] it was envisaged that cyclopropylacrylamide *trans*-**517** could be accessed in short order by difunctionalisation of isocyanate **525**. The proposed key step involves Curtius rearrangement of **524**, as in Mendoza's report, to form isocyanate **525**. This could be reacted with a nucleophilic vinyl reagent (such as vinyl lithium) and then with an electrophilic methylating reagent such as iodomethane to give cyclopropylacrylamide ***trans*-517**. Successful execution of this proposal would provide cyclopropylacrylamide ***trans*-517** in three steps from commercially available silane **516**.

3.2.4.5.2 (7+1) carbonylative cycloaddition of silylmethyl-substituted cyclopropylacrylamides

Both diastereomers of cyclopropylacrylamide **517** were tested in the (7+1) carbonylative cycloaddition using a sealed reaction vessel in accordance with the studies in Section 3.2.1.2. Under the

previously optimised (7+1) carbonylative cycloaddition conditions, cyclopropylacrylamide ***trans*-517** formed desired azocane **518** in 7% yield (Entry 1), although the product was stable under the reaction conditions, suggesting that the reaction could be optimised. Initially, it was discovered that by lowering the reaction temperature (130 °C from 150 °C) and running it for four days, azocane **518** was formed in 24% yield with 32% of the starting material remaining (Entry 2). A ligand screen of various triarylphosphines and triarylarsines gave interesting results. Notably, the use of electron-rich ligands, such as triphenylphosphine, provided low yields of azocane **518** (16%), but very high recovery of the starting material (82%) (Entry 3). In this case the ligand is presumably stabilising a catalytic intermediate, thereby preventing non-specific degradation. Unfortunately, further attempts to optimise the use of electron-rich ligands were not fruitful. Triphenylarsine provided azocane **518** in 22% yield with 24% of cyclopropylacrylamide ***trans*-517** remaining, and was therefore chosen for further optimisation (Entry 4).



***trans*-517** **518**

Entry	Ligand	Additive	T	time	Yield[a]	517
1	$P(p\text{-}CNC_6H_4)_3$	*N*-methyltrifluoroacetamide	150 °C	48 h	7%	12%
2	$P(p\text{-}CNC_6H_4)_3$	*N*-methyltrifluoroacetamide	130 °C	96 h	24%	32%
3	PPh_3	*N*-methyltrifluoroacetamide	130 °C	72 h	16%	82%
4	$AsPh_3$	*N*-methyltrifluoroacetamide	140 °C	40 h	22%	24%
5	$AsPh_3$	benzoic acid	140 °C	40 h	32%	8%
6	$AsPh_3$	benzamide	140 °C	40 h	31%	20%
7	**$AsPh_3$**	**fumaric acid[b]**	**140 °C**	**66 h**	**35%**	**0%**
8[c]	**$AsPh_3$**	**fumaric acid[b]**	**140 °C**	**70h**	**30%**	**0%**

[a]*In-situ* NMR yield measured against an internal standard; [b]25 mol%; [c]Using ***cis*-517**.

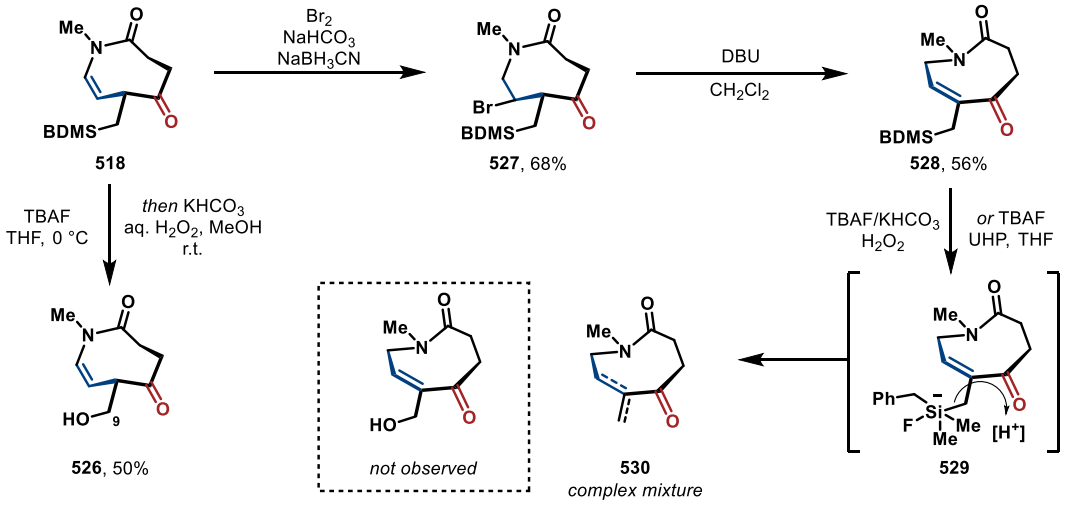
Table 15: Selected results from the optimisation of the Rh(I)-catalysed (7+1) carbonylative cycloaddition of ***trans*-517**.

Next, alternative additives (to *N*-methyltrifluoroacetamide) were screened because additives were previously shown to have a dramatic effect on the yield of (7+1) carbonylative cycloadditions (Section 3.2.1.2). During these studies, benzoic acid (32% yield, Entry 5), benzamide (31% yield, Entry 6) and fumaric acid (35% yield, Entry 7) were found to provide a greater yield of azocane **518**. The conditions shown in Entry 7 were carried out on multi-mmol scale with no significant decrease in yield, so were chosen in order to investigate the following steps. Additionally, *cis*-1,2-disubstituted cyclopropylacrylamide ***cis*-517** reacted under the newly optimised conditions to give azocane **518** in 30% yield. Further optimisation of the (7+1) carbonylative cycloaddition of cyclopropylacrylamides

517 is clearly required and should focus on a further in-depth survey of ligands and additives. It is worth noting the significant electronic effect that the silylmethyl-substituent had on the reactivity the cyclopropylacrylamide as illustrated by the substantially different conditions (temperature, ligand and additive) necessary for an efficient (7+1) carbonylative cycloaddition when compared to alkyl-substituted cyclopropylacrylamide **402** (Section 3.2.1.2).

3.2.4.5.3 Validation of the Tamao-Fleming approach

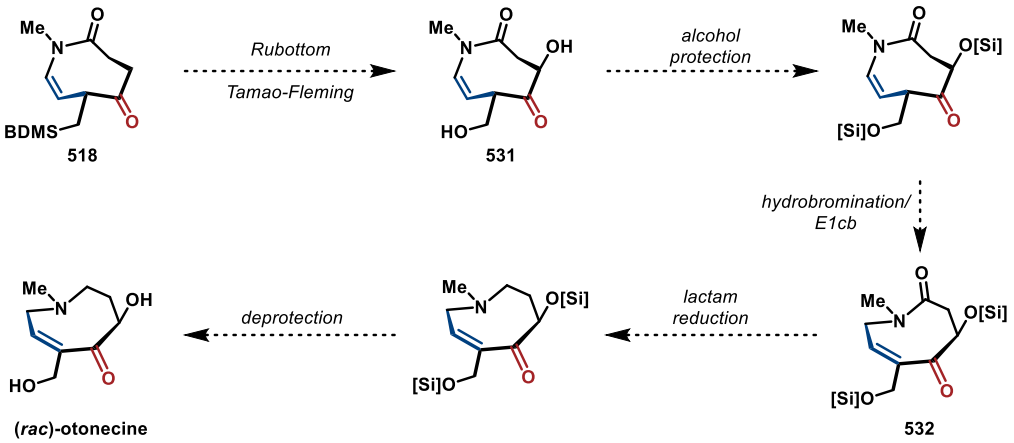
The optimised conditions for the (7+1) carbonylative cycloaddition of cyclopropylacrylamides **517** provided sufficient quantities of azocane **518** to attempt the Tamao-Fleming oxidation with the aim of identifying the ideal point in the synthesis to carry out the transformation. To begin, azocane **518** was treated under the standard conditions for Tamao-Fleming oxidation (TBAF *then* H_2O_2/NaOH) (Scheme 122). Encouragingly, this provided C9-alcohol **526** in 50% yield, which served as the first time that the C9-alcohol has been installed in the presence of the ketone during these studies. Next, the C2-alkene of azocane was isomerised to the C1-position, by the previously developed two step hydrobromination/E1cB elimination sequence, providing enone **528** in 35% yield over the two steps. Under the standard conditions (TBAF/hydrogen peroxide) for Tamao-Fleming oxidation, enone **528** gave a mixture of alkenes **530**, likely by protodesilylation of the C9-position of proposed intermediate **529**, instead of the benzylic position. Trost and co-workers have developed anhydrous conditions (TBAF/urea hydrogen peroxide) for the Tamao-Fleming oxidation of benzylsilanes, specifically to avoid protodesilylation.[318] However, under the anhydrous conditions, enone **528** also reacted to form alkenes **530**. Nevertheless, the synthesis of C9-alcohol **526**, by Tamao-Fleming oxidation of azocane **518** marks a significant milestone towards the total synthesis of otonecine, whereby conditions for three out of the four post-cycloaddition transformations had been identified.



Scheme 122: Validation of the Tamao-Fleming strategy by the synthesis of C9-alcohol **526**.

3.2.5 Studies towards the total synthesis of (*rac*)-otonecine

At this stage in the project, efforts were directed towards completing the total synthesis of (*rac*)-otonecine. The step order shown in Scheme 123 was deduced based on the findings detailed in the previous sections. Firstly, azocane **518** would undergo a two step Rubottom oxidation then Tamao-Fleming oxidation to install the C7- and C9-alcohols of azocane **531**. These would both be protected as TBS-ethers in order to reduce the polarity of the molecule and provide steric shielding of the C8-ketone in preparation for the two remaining steps, which uses reducing agents. Next, alkene isomerisation by the hydrobromination/E1cB elimination sequence would provide enone **532** and set the stage for the final lactam reduction and deprotection steps to access (*rac*)-otonecine.

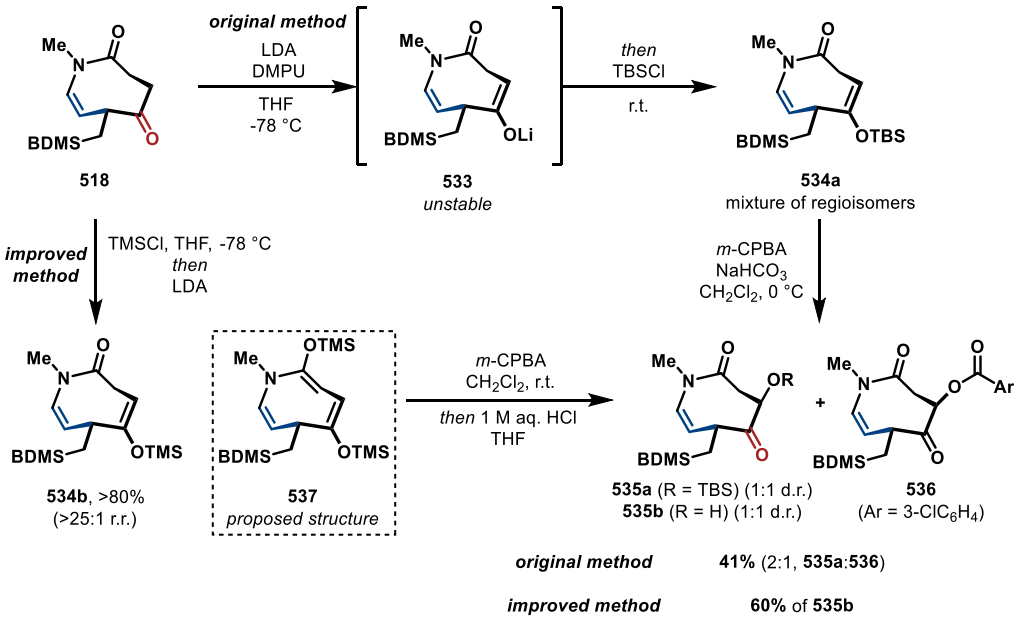


Scheme 123: Proposed order of the post-cycloaddition transformations of azocane **518**.

3.2.5.1 Synthesis of an advanced lactam intermediate

The previously developed conditions for the generation of kinetic silyl enol ethers from azocanes (Section 3.2.2.1) provided poor results when applied to azocane **518** (Scheme 124). Lithium enolate **533**, formed by deprotonation of azocane **518** with LDA/DMPU, was observed to be unstable in solution at -78 °C, and the subsequent reaction with TBSCl was very slow, providing an impure mixture of silyl enol ether **534a** regioisomers. Additionally, Rubottom oxidation of crude silyl enol ether **534a** was poor yielding due to the formation of significant quantities of C7-benzoate **536** (*via* a acetal intermediate, see **430**, Scheme 95) (41% combined yield, 2:1, **535a**:**536**). Improvements to the two step procedure were made by reversing the order of addition of reagents in order to limit the lifetime of lithium enolate **533**, and by employing TMSCl as a more reactive electrophile. Therefore, LDA was added to a mixture of azocane **518** and TMSCl at -78 °C, which immediately formed silyl enol ether **534b** as a single regioisomer. Importantly, the addition of LDA was monitored closely by TLC to avoid formation of a new non-polar compound, likely by further reaction of silyl enol ether **534b**. The structure of the new side-product was not confirmed, but was proposed to be bis-silyl enol ether **537**.

This new method routinely provided silyl enol ether **534b** in >80% yield as a single regioisomer, which was carried through to the Rubottom oxidation without column chromatography.

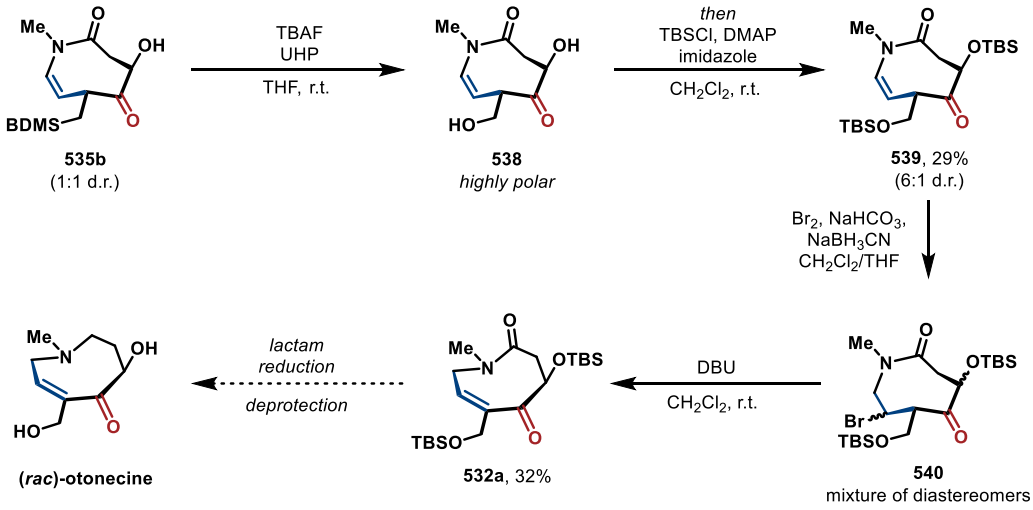


Scheme 124: Development of a reliable two step Rubottom oxidation sequence for the installation of the C7-alcohol onto azocane **528**.

The low yields obtained in the Rubottom oxidation of TBS-silyl enol ether **534a** was partly due to the competitive formation of C8-hemiacetal **536**. A report by Wang and co-workers suggests that hemiacetal formation is promoted by the presence of base in the Rubottom oxidation, which extends the lifetime of oxonium intermediate **431** (see Scheme 95B, Section 3.2.2.1).[321] Therefore, Rubottom oxidation of silyl enol ether **534b** was carried out in the absence of sodium bicarbonate, which successfully reduced the formation of a hemiacetal analogue. Finally, the crude reaction mixture was hydrolysed under acidic conditions to provide C7-alcohol **535b** in 60% yield over the two steps, as a 1:1 mixture of diastereomers (separable by chromatography). The diastereoselectivity of the Rubottom oxidation (1:1 d.r.) will need to be addressed for the asymmetric synthesis of otonecine, however it was inconsequential for the synthesis of (*rac*)-otonecine, so a mixture of both diastereomers was carried through to the next step.

Tamao-Fleming oxidation of C7-hydroxyazocane **535b** proved to be challenging (Scheme 125). Under standard aqueous conditions (TBAF/hydrogen peroxide), C7-hydroxyazocane **535b** reacted rapidly to form diol **538**, which was visible by TLC. However, diol **538** is very polar and highly water soluble, which complicated its isolation. Attempts to isolate diol **538** from the aqueous phase during the work-up required repeated extraction of the aqueous phase, which contaminated diol **538** with copious amounts of tetrabutyl ammonium salts. Furthermore, concentration of the resulting

organic extracts caused the degradation of diol **538**, presumably due to the presence of residual peroxide.



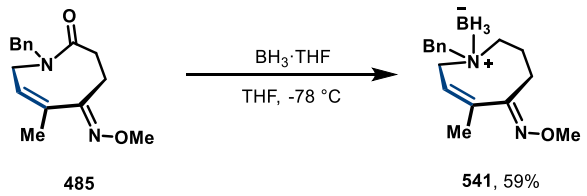
Scheme 125: Synthesis of enone **532a** from azocane **535b**.

Focus turned to the anhydrous Tamao-Fleming conditions (TBAF/urea hydrogen peroxide) developed by Trost.[318] Under these conditions, C9-alcohol **535b** was converted to diol **538** in three hours, which was isolated as a mixture with tetrabutylammonium salts upon reduction of residual peroxide and extensive extraction of the aqueous phase. Attempts to remove the tetrabutylammonium salts by precipitation, or column chromatography failed due to the high polarity of the diol. Therefore, crude diol **538** was silylated to afford bis-TBS ether **539** in 29% yield from C9-alcohol **535b**, which was isolated after a standard aqueous work-up and column chromatography. Hydrobromination of bis-TBS ether **539** proceeded smoothly to provide C2-bromide **540** as an inconsequential mixture of diastereomers (not characterised). E1cB elimination from *bis*-TBS ether **540** was slow due to the sterically congested nature of the C1-position, which resulted in the unwanted isomerisation of the alkene back to the C2-position becoming competitive. This was avoided by stopping the reaction early at the expense of low yields of enone **532a** (32% yield). Nevertheless, sufficient quantities of enone **532a** were obtained through this route to attempt the penultimate lactam reduction.

3.2.5.2 Attempts to reduce the lactam of an advanced intermediate

Up until this point, the lactam reduction step had received only sporadic attention, but this revealed several valuable and unexpected observations. As was described in Section 3.2.2.2, lactam reduction in the presence of the C2-alkene (as in **427a**, Scheme 96C) often resulted in partial reduction and ring-opening of the strained azocane ring. However, some success was realised on treatment of protected azocane **434** with BH_3·THF, which provided aminoalcohol **451** (Section 3.2.3.3.1). Later in the project, BH_3·THF successfully reduced the lactam of oxime **485**, providing amine·BH_3 adduct **541**

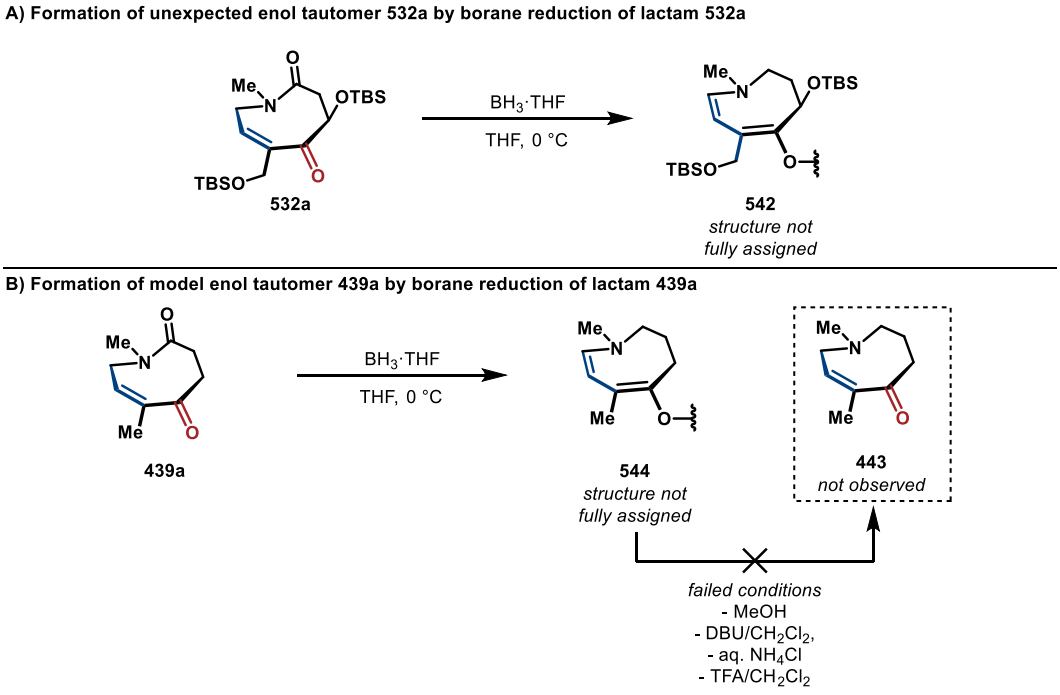
in 59% yield (Scheme 126). Borane-amine adducts have found use as amine protecting groups in the synthesis of complex molecules and might be useful in the current context by masking the N-C8 transannular interaction.[322]



485 **541**, 59%

Scheme 126: Borane reduction of the lactam of oxime **485** to form amine-borane adduct **541**.

With this information in hand, the penultimate lactam reduction of bis-TBS ether **532a** was attempted using BH_3·THF. In the event, the lactam of **532a** underwent a rapid reaction with BH_3·THF, but failed to provide protected otonecine **543**. Instead, a structurally related compound was isolated, the structure of which is yet to be fully assigned. Preliminary data (^{1}H, ^{13}C, COSY, HSQC, HMBC, HRMS, *see experimental*) suggests that the unknown product contains the structural motif shown in **542** where the lactam has been fully reduced and the C1-alkene has migrated to form an extended enol structure.

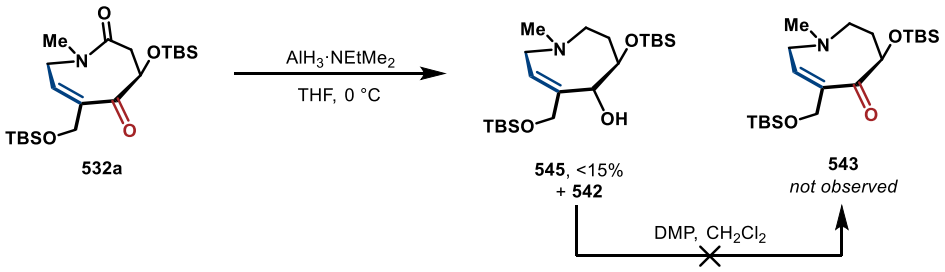


Scheme 127

To avoid consuming valuable bis-TBS ether **532a**, model enone **439a** was employed in order to further investigate the lactam reduction step. Lactam reduction of model enone **439a** with BH_3·THF proceeded in a similar fashion to above, forming a compound bearing the structural motif of **544** (Scheme 127B). Enol **544** was then subjected to a range of conditions in an attempt to promote formation of desired enone **443**. Enol **544** was found to be stable to protic solvents (methanol), basic

conditions (DBU) and aq. NH_4Cl, but rapidly degraded when treated with trifluoroacetic acid (standard extraction methods for otonecine involves the use of strongly acidic conditions, including refluxing aq. 10% HCl[323]). Having failed to form bis-TBS otonecine **543** using BH_3·THF, several alternative chemoselective lactam reduction conditions (including $Ir(CO)Cl(PPh_3)_2$/TMDSO,[261] Lawesson's reagent/Raney nickel and $Zn(OAc)_2$/$(EtO)_3SiH$[324]) were screened using model compound **439a**, but none of these provided enone **443**.

The remaining quantity of bis-TBS ether **532a** was reacted with alane (AlH_3), which exhibits similar reactivity to borane and is known to reduce challenging lactams in the presence of other reducible functionality (Scheme 128).[325] In the event, bis-TBS ether **532a** was consumed rapidly, forming the previously observed enol **542** as well as a C8-reduction product **545**. An attempt to reoxidise the C8-alcohol of alcohol **545** failed to form bis-TBS otonecine **543**.



Scheme 128: Formation of alcohol **545** by the reduction of enone **532a** using alane.

At this point, studies towards the total synthesis of (*rac*)-otonecine were paused due to time constraints. The penultimate lactam reduction step proved to be challenging, often resulting in the formation of an unidentified side-product tentatively containing the structural motif **542**. Complete structural elucidation of this side-product might aid in the identification of a suitable method for the reduction of the lactam moiety of bis-TBS ether **532a**.

3.3 Studies towards the total synthesis of the C_{10} dicarboxylic necic acids

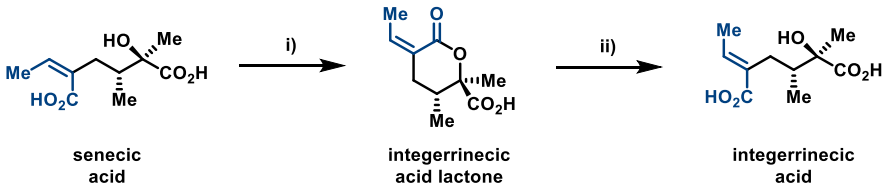
The research described so far in Chapter 3 demonstrates significant progress towards the total synthesis of otonecine. Therefore, parallel studies were initiated to investigate the synthesis of the C_{10} dicarboxylic necic acids, with the goal of achieving the first total synthesis of an otonecine-type macrocyclic diester. This section begins with a review of previous synthetic efforts towards the C_{10} necic acids. Then, in Section 3.3.3, research carried out at Bristol towards the asymmetric synthesis of some of these compounds will be presented.

3.3.1 Previous syntheses of C_{10} dicarboxylic necic acids

The C_{10} dicarboxylic necic acids have received less synthetic attention than the necic bases with most studies targeting integerrinecic acid and its diastereomers (Figure 4). Nevertheless, several distinct strategies have emerged for the preparation of racemic and enantiomerically enriched dicarboxylic necic acids, and these strategies are discussed herein. Additionally, most of these reports were carried out as part of a synthesis of a retronecine-type macrocyclic diester, lessons from which may prove valuable for the current project. Therefore, the strategies employed to form PA macrocyclic diesters are included.

3.3.1.1 Isomerisation of senecic acid

During early studies towards determining the structure of the C_{10} dicarboxylic necic acids, Richardson and Warren observed that senecic acid (isolated from a natural source) underwent lactonisation and concomitant alkene isomerisation when treated with dilute hydrochloric acid to form integerrinecic acid lactone (Scheme 129).[326] This finding was confirmed by hydrolysis of the resulting lactone, which provided integerrinecic acid. The authors concluded that the *E*-alkene geometry is more stable than the Z-alkene geometry in this class of molecules. Integerrinecic acid lactone, and it's diastereomers, has since become a popular intermediate in the synthesis of C_{10} dicarboxylic acids.[327]

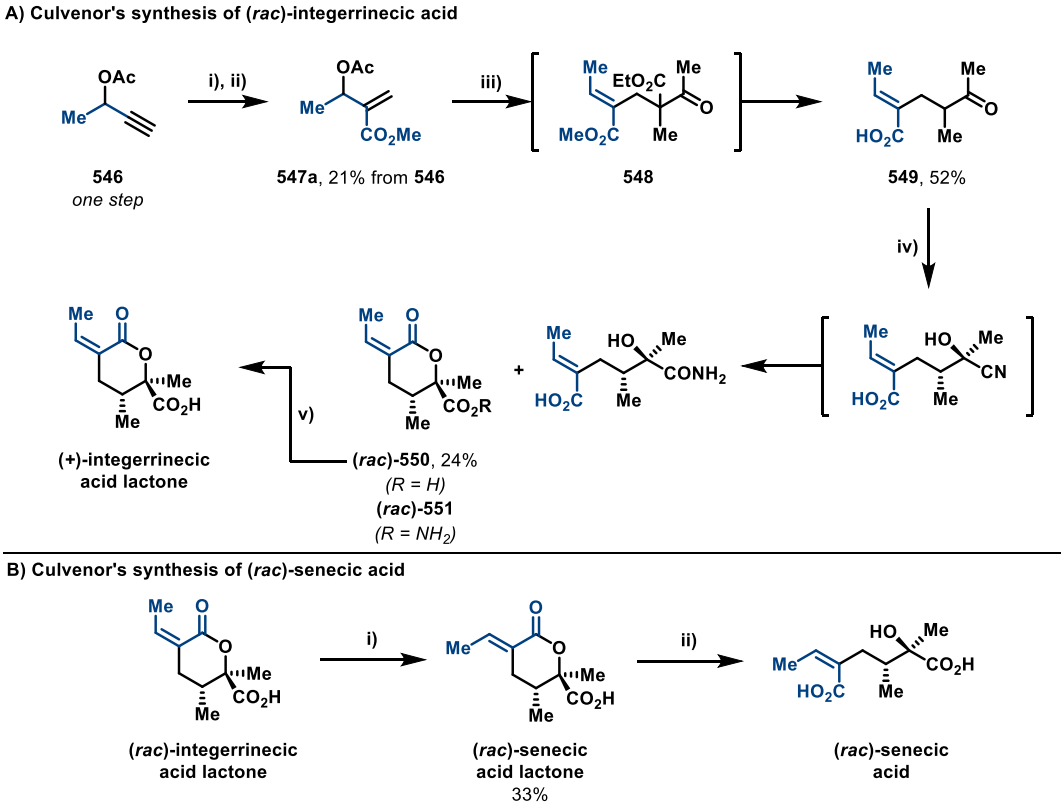


Scheme 129: Acid-mediated conversion of senecic acid to integerrinecic acid. *Reagents and conditions (some details were not provided by the authors)*: i) dilute HCl; ii) aq. NaOH, reflux.

3.3.1.2 Michael addition strategy for the synthesis of integerrinecic acid and senecic acid

Culvenor and Geissman completed the first formal total synthesis of (+)-integerrinecic acid and (*rac*)-senecic acid, in 1961 (Scheme 130A).[328] The synthesis of (+)-integerrinecic acid began with propargylic acetate **546**, which was subjected to an unselective $Ni(CO)_4$-mediated hydrocarboxylation,

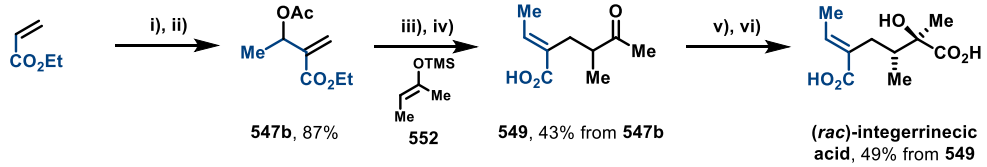
providing branched α,β-unsaturated ester **547a** in 21% yield, after esterification. Michael addition of ethyl methylacetoacetate to α,β-unsaturated ester **547a** formed diester **548**, which was immediately advanced to ketoacid **549** by hydrolysis. Hydrocyanation of ketoacid **549** and hydrolysis of the resulting nitrile formed a complex mixture of three species from which desired lactone **(*rac*)-550** could be separated in 24% yield. Racemic lactone **(*rac*)-550** was resolved by crystallisation with brucine thus completing a formal seven step total synthesis of (+)-integerrinecic acid. Culvenor also demonstrated that the *Z*-alkene of integerrinecic acid lactone could be isomerised to the *E*-alkene by irradiation with ultraviolet light to form the senecic acid lactone (Scheme 130B). Hydrolysis of senecic acid lactone formed (*rac*)-senecic acid in eight steps overall.



Scheme 130: A) *Reagents and conditions (some details were not provided by the authors)*: i) $Ni(CO)_4$, EtOH/AcOH/H_2O, reflux, 1 h, 25%; ii) CH_2N_2, Et_2O, 0 °C, 84%; iii) ethyl methylacetoacetate, NaOEt, EtOH, r.t., 1.5 h *then* 1 M aq. NaOH, r.t., 5 h; iv) NaCN, H_2O *then* conc. HCl, 100 °C, 3 h, 24% of **(*rac*)-550**; v) Resolution achieved by crystallisation with brucine. B) *Reagents and conditions (some details were not provided by the authors)*: hυ, EtOH, 10 h, 33%; ii) 1 M aq. NaOH, 1 h.

In 1982, Drewes and Emslie published a short and efficient six step synthesis of (*rac*)-integerrinecic acid, adopting a similar strategy to Culvenor (Scheme 131).[329] Acrylate **547b** was formed in 87% yield by an improved method involving Baylis-Hillman reaction between ethyl acrylate and acetaldehyde, and acetylation. Acrylate **547b** underwent a Michael addition /elimination sequence with

silyl enol ether **552** to form ketoacid **549**, which was reacted with sodium cyanide and then concentrated hydrochloric acid to form (*rac*)-integerrinecic acid.

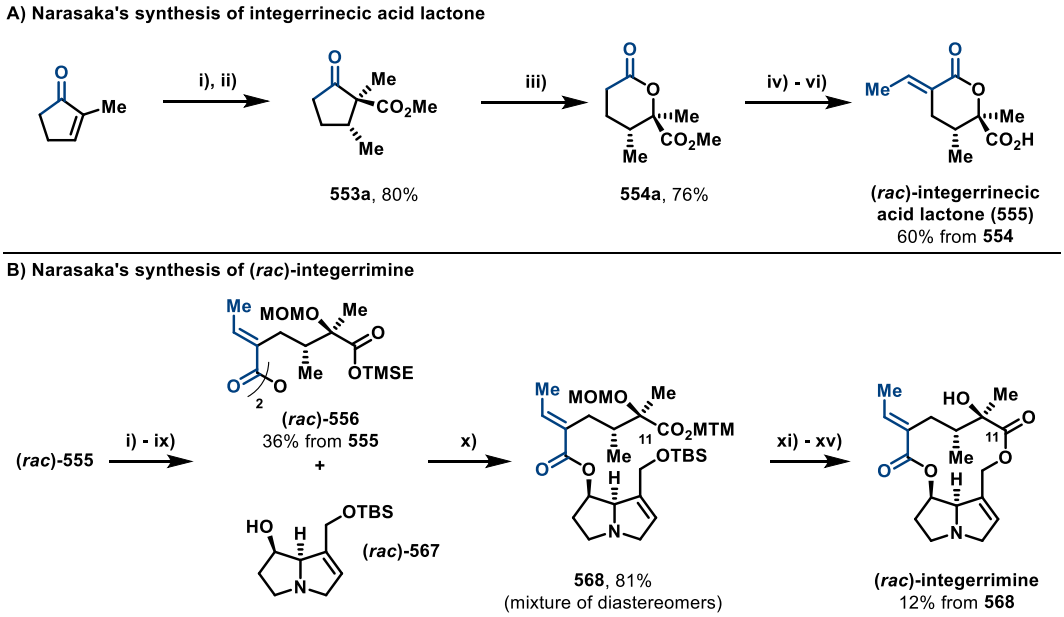


Scheme 131: Drewes and Emslie's synthesis of (*rac*)-integerrinecic acid. *Reagents and conditions (some details were not provided by the authors)*: i) acetaldehyde, DABCO, r.t., 7 d, 94%; ii) Ac_2O, conc. H_2SO_4, 0 °C, 30 min, 93%; iii) **552**, $TiCl_4$, CH_2Cl_2, -78 °C, 3 h, 63%; iv) 1 M aq. KOH, r.t., 12 h, 69%; v) NaCN, 0.01 M aq. H_2SO_4, H_2O, 0 °C, 78%; vi) conc. HCl, 5 °C, 12 h, 63%.

3.3.1.3 Baeyer-Villiger oxidation for the formation of lactones

In 1982, Narasaka and Uchimaru published an alternative method for the synthesis of integerrinecic acid lactone, employing a Baeyer-Villiger oxidation to access functionalised lactone **554a** (Scheme 132A).[330-332] The synthesis began with a one-pot conjugate addition/carboxylation and methylation of 2-methyl-2-cyclopentenone, which provided cyclopentanone **553a** in 80% yield over the two steps. Regioselective Baeyer-Villiger oxidation of **553a** formed lactone **554a** in 76% yield. The exocyclic alkene unit was installed by a two step aldol condensation to form integerrinecic acid lactone **555** (60% yield from **554a**), thus completing a seven step formal synthesis of (*rac*)-integerrinecic acid. Lactone **554a** and the two step aldol condensation have been employed in several syntheses of necic acids.

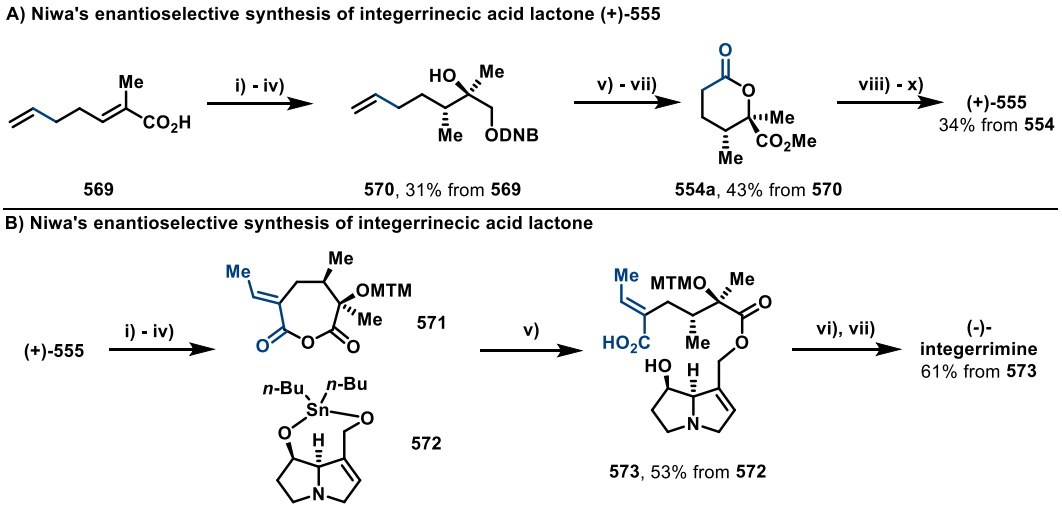
Narasaka and co-workers simultaneously published the first total synthesis of the retronecine-type macrocyclic diester, (*rac*)-integerrimine (Scheme 132B).[331-332] The synthesis required integerrinecic acid lactone **(*rac*)-555** to undergo nine further manipulations to reach protected anhydride **(*rac*)-556**, which was coupled with protected retronecine **(*rac*)-567** to give monoester **568**. Macrolactonisation was achieved by TBS-deprotection of the C9-alcohol of monoester **568** and oxidation of the methyl thiomethylester, which served to activate the C11-ester to cyclisation. Final deprotection steps formed (*rac*)-integerrimine, which was separated from its unnatural diastereomer.



Scheme 132: A) *Reagents and conditions (some details were not provided by the authors)*: i) Me_2Culi, Et_2O, -20 °C, 3 h *then* dry ice, 1.5 h, 80%; ii) CH_2N_2, Et_2O; iii) *m*-CPBA, Li_2CO_3, CH_2Cl_2, reflux, 13.5 h; iv) LDA, THF, -78 °C, 15 min *then* acetaldehyde, -40 °C, 1 h; v) 2-fluoro-1-methylpyridinium *p*-toluenesulfonate, CH_2Cl_2, NEt_3, 0 °C, overnight. B) *Reagents and conditions (some details were not provided by the authors)*: i) 2-chloro-1-methylpyridinium iodide, CH_2Cl_2, 2-(trimethylsilyl)ethanol, NEt_3, r.t., overnight, 98%; ii) LiOH, 28% aq. H_2O_2, THF/H_2O, r.t., 3 h, 71%; iii) chloromethyl methyl sulfide, NaI, $(i\text{-Pr})_2NEt$, 1,2-dimethoxyethane, r.t., overnight *then* reflux, 1 h, 92%; iv) chloromethyl methyl ether, NaI, $(i\text{-Pr})_2NEt$, 1,2-dimethoxyethane, reflux, 12 h, 88%; v) TBAF, THF, r.t., 3.5 h, 93%; vi) 28% aq. H_2O_2, 0.1 M aq. $(NH_4)_6Mo_7O_{24}$, acetone/H_2O, r.t., 3 h, 89%; vii) chloromethyl methyl sulfide, NaI, $(i\text{-Pr})_2NEt$, 1,2-dimethoxyethane, r.t., 6 h, 86%; viii) 1 M aq. NaOH, 1,2-dimethoxyethane, r.t., 5 h, 100%; ix) 2-chloro-1-methylpyridinium iodide, NEt_3, CH_2Cl_2, r.t., 24 h, 91%; x) *n*-BuLi, DMAP, THF, 0 °C to r.t., 4.5 h; xi) NH_4F, MeOH/H_2O, 60 °C, 6 h, 82%; xii) 28% aq. H_2O_2, 0.1 M aq. $(NH_4)_6Mo_7O_{24}$, EtOH/H_2O, r.t., 1.5 h, 73%; xiii) Ph_3CLi, THF, -78 °C, 2 h, 41%; xiv) 1 M aq. H_2SO_4, Zn, 1,2-dimethoxyethane, r.t., 1 h, 59%; xv) 1 M aq. H_2SO_4, 1,2-dimethoxyethane, 40 °C, 2.5 h, 86%.

3.3.1.4 Niwa's enantioselective synthesis of (+)-integerrinecic acid and (-)-integerrimine

Niwa, Yamada and co-workers reported the first enantioselective synthesis of (+)-integerrinecic acid and (-)-integerrimine in 1986 (Scheme 133A).[333-335] Initially, carboxylic acid **569** was reduced in preparation for Sharpless asymmetric epoxidation (71% yield, 96% e.e.). Nucleophilic ring opening of the resulting epoxide with Me_3Al provided alcohol **570**. Oxidative cleavage of the terminal alkene caused a spontaneous lactonisation forming lactone **554a**, which was advanced to integerrinecic acid lactone **555** by a two step aldol condensation resulting in a formal twelve step synthesis of (+)-integerrinecic acid.

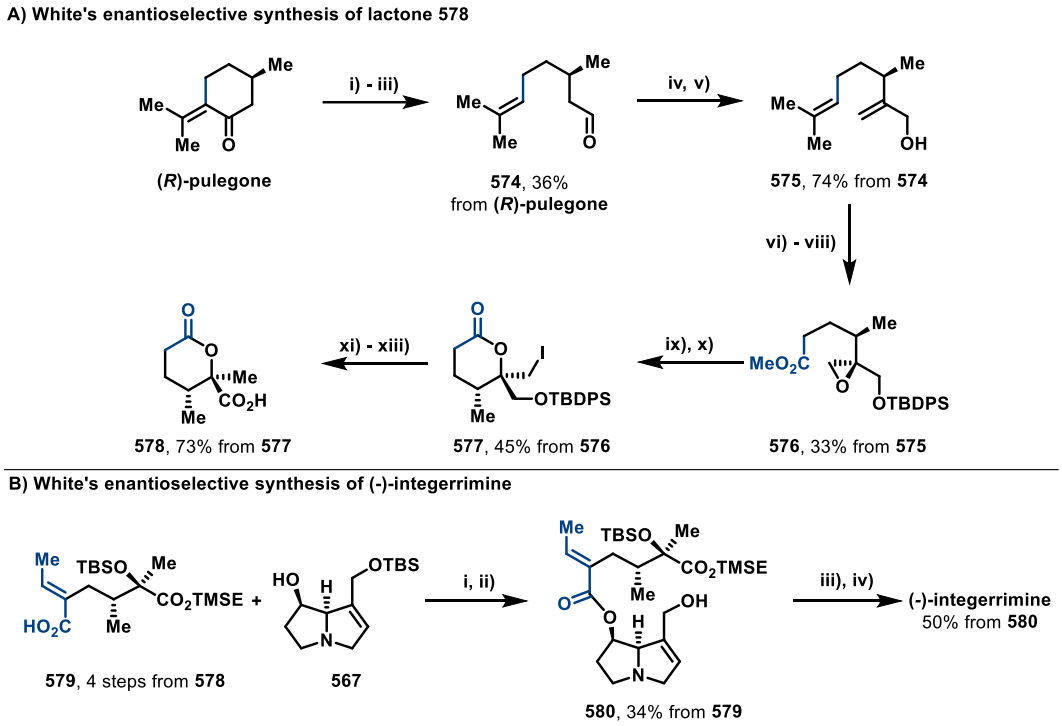


Scheme 133: A) *Reagents and conditions (some details were not provided by the authors)*: i) $LiAlH_4$, THF, r.t., 12 h, 69%; ii) Ti(*i*-OPr)$_4$, diethyl (+)-tartrate, *t*-BuOOH, CH_2Cl_2, -25 °C, 3 h, 71%, 96% e.e.; iii) Me_3Al, hexane, 0 °C, 2 h, 72%, iv) 3,5-dinitrobenzoyl chloride, pyridine, 0 °C to r.t., 3 h, 88%; v) $RuCl_3.3H_2O$, $NaIO_4$, pH 7 phosphate buffer, CCl_4/MeCN, r.t., 1 h *then* *p*-TSA, PhH, reflux, 1 h, 99%; vi) NaOMe, MeOH, r.t., 30 min *then* *p*-TSA, PhH, reflux, 1 h, 76%; vii) $RuCl_3.3H_2O$, $NaIO_4$, pH 7 phosphate buffer, CCl_4/MeCN, 0 °C to r.t., 2.5 h *then* CH_2N_2, Et_2O, 79%; viii) LDA, THF, -78 °C, 1 h *then* acetaldehyde, -30 °C, 2 h; ix) MsCl, pyridine, r.t., 2 h; x) DBU, PhH, reflux, 2 h, 34% over three steps. A) *Reagents and conditions (some details were not provided by the authors)*: i) NaOMe, MeOH, r.t., 2.5 h; ii) Ac_2O, DMSO, 40 °C, 24 h, 61% over two steps; iii) KOH, MeOH, H_2O, reflux, 1 h, 88%; iv) DCC, CH_2Cl_2, r.t., 2 h; v) (+)-retronecine, Bu_2SnO, 4Å MS, PhH, reflux, 19 h *then* **571**, r.t., 3 h, 98% over two steps from **572**; vi) 2,4,6-trichlorobenzoyl chloride, NEt_3, THF, r.t., 2 h *then* DMAP, PhMe, reflux, 3.5 h, 75%; vii) $Ph_3C{\cdot}BF_4$, CH_2Cl_2, r.t., 1.5 h, 81%.

Niwa, Yamada and co-workers employed a novel route to the synthesis of (-)-integerrimine (Scheme 133B).[334-335] Integerrinecic acid lactone **555** was transformed into cyclic anhydride **571** over four steps, and this was coupled regioselectively with a tin derivative of retronecine, **572**, providing monoester **573** in 53% yield. Yamaguchi macrolactonisation and MTM-deprotection formed (-)-integerrimine. The retronecine-type macrocyclic diester, senecionine, was later synthesised by an analogous route *via* UV-light induced isomerisation of the alkene of lactone **555** (see Scheme 130, B).[336]

White and Jayasinghe reported an alternative asymmetric synthesis of integerrinecic acid lactone **555** in 1988, which employed the natural product, (*R*)-pulegone. Initially, (*R*)-pulegone was advanced to citronellal **574** by a known three step sequence (Scheme 134A).[337-338] Citronellal **574** then underwent methylenation and Luche reduction to give allylic alcohol **575**, which was transformed into epoxide **576** by a diastereoselective Sharpless epoxidation. Acid-promoted lactonisation and iodination of epoxide **576** provided lactone **577**. Finally, radical reduction of the iodide and oxidation of the primary alcohol formed lactone **577**, thereby completing a formal 18 step total synthesis of (+)-integerrinecic acid.

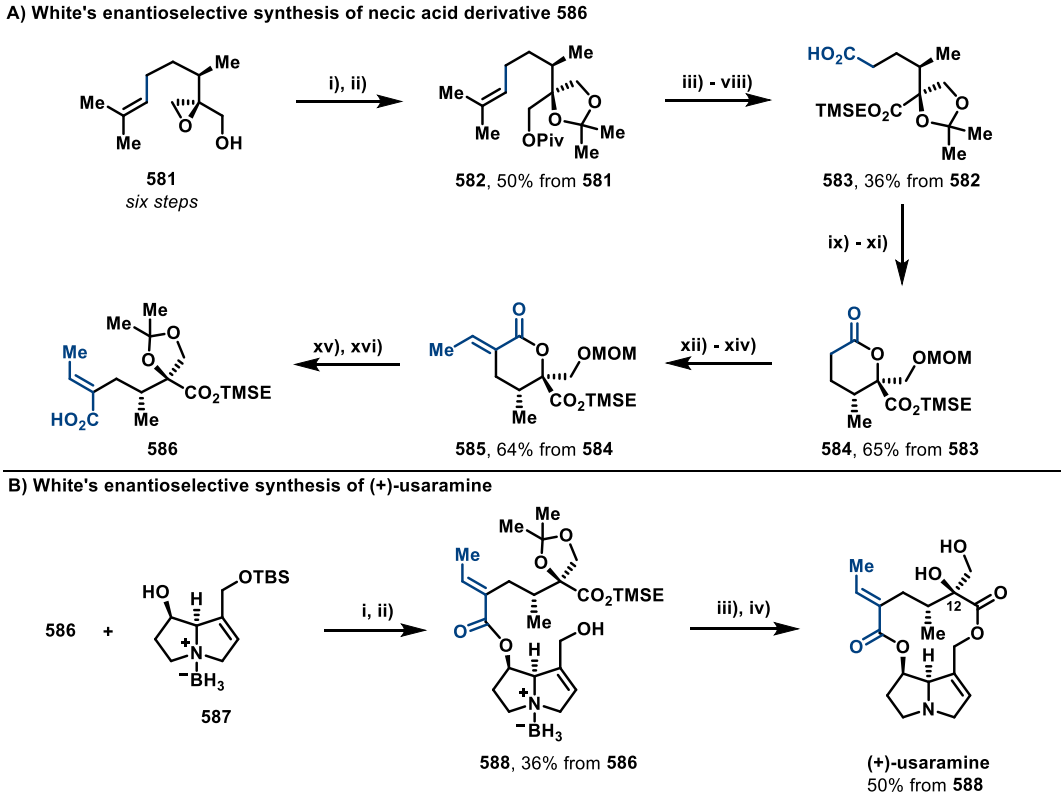
White and co-workers also published a synthesis of (-)-integerrimine from protected integerrinecic acid **579** and TBS-protected retronecine **567** (Scheme 134B).[338] Initial esterification to form monoester **580** was achieved by activation of the carboxylic acid of necic acid **579** with diethyl chlorophosphite, which was coupled with deprotonated retronecine derivative **567**. In this case, macrolactonisation was achieved by chemoselective deprotection of the TMSE-ester moiety, activation of the C9-alcohol as the mesylate and intramolecular S_N2-substitution. TBS-deprotection formed (-)-integerrimine in four steps from the necic acid and base components.



Scheme 134: A) *Reagents and conditions (some details were not provided by the authors)*: i) HCl (g), -10 °C to r.t., 11 h *then* aq. NaOH, r.t., overnight, 53%; ii) $LiAlH_4$, Et_2O, 0 °C, 1 h, 97%; iii) PCC, NaOAc, CH_2Cl_2, r.t., 2 h, 70%; iv) LDA, THF, -78 °C *then* Eschenmoser's salt, -78 °C to r.t., 5 h *then* MeI, MeOH, 0 °C to r.t., overnight *then* 5% aq. $NaHCO_3$, r.t., 16 h, 78%; v) $CeCl_3{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C, 10 min, 95%; vi) Ti(*i*-OPr)$_4$, diisopropyl (+)-tartrate, cumene hydroperoxide, 3Å MS, CH_2Cl_2, -5 °C, 8 h, 81%; vii) TBDPSCl, imidazole, DMAP, DMF, r.t., 5 h, 90%; viii) O_3, CH_2Cl_2, -78 °C, 45 min *then* CrO_3, -10 °C, 45 min *then* CH_2N_2, Et_2O, 45%; ix) trifluoroacetic acid, $CHCl_3$, -10 °C to 0 °C, 1 h, 50%; x) PPh_3, imidazole, I_2, PhH, reflux, 1.5 h, 90%; xi) *n*-Bu_3SnH, AIBN; xii) TBAF, THF; xiii) $RuCl_3.3H_2O$, $NaIO_4$, pH 7 phosphate buffer, CCl_4/MeCN/H_2O, r.t., 3 h, 73%. B) *Reagents and conditions (some details were not provided by the authors)*: i) $(EtO)_2POCl$, NEt_3, THF, 0 °C to r.t., 3 h *then* **567**, DMAP, *n*-BuLi, 0 °C to r.t., 5 h, 51%; ii) NH_4F, MeOH/H_2O, 60 °C, 4 h, 67%; iii), MsCl, CH_2Cl_2, 0 °C, 30 min *then* TBAF, MeCN, r.t., 30 min, 75%; iv) 48% aq. HF, MeCN, r.t., 12 h, 67%.

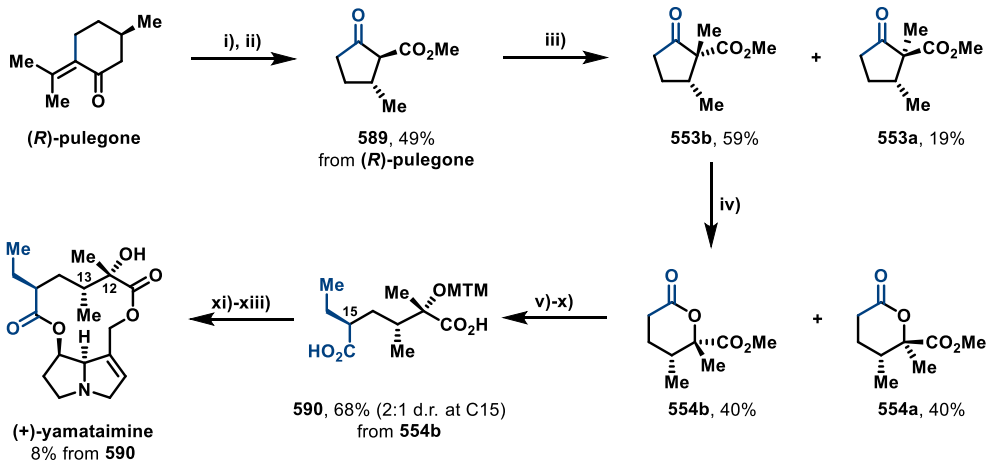
White and co-workers also reported a synthesis of (+)-usaramine, the necic acid portion of which contains an additional C12-hydroxymethyl group (Scheme 135A).[338] This functionalised necic acid is also found as part of the otonecine-type macrocyclic diester, hydroxysenkirkine (Figure 4D). Epoxide **581** was initially prepared in six steps *via* by Sharpless epoxidation of allylic alcohol **575**.

Lewis acid mediated ring opening of the epoxide with pivalic acid and ketal protection provided ketal **582**. Several redox transformations were required to advance ketal **582** to carboxylic acid **583**, which then underwent ketal deprotection and lactonisation to form six-membered lactone **584**. Lactone **584** was advanced to suitable coupling partner **586** in five steps, including aldol addition/elimination and ring opening of the lactam. Therefore, protected necic acid coupling partner **586** was synthesised in 22 steps from (*R*)-pulegone. White's synthesis of (+)-usaramine employed *N*-protected retronecine **587** in order to avoid oxidative aromatisation of the necic base during the esterification step (Scheme 135B). The remainder of the macrolactonisation sequence proceeded as in White's synthesis of (-)-integerrimine (Scheme 134B).



Scheme 135: A) *Reagents and conditions (some details were not provided by the authors)*: i) pivalic acid, Ti(O*i*-Pr)$_4$, PhH, r.t., 20 min, 51%; ii) 2,2-dimethoxypropane, CSA, CH_2Cl_2, r.t., 5 h, 98%; iii) $LiAlH_4$, Et_2O, reflux, 1 h, 90%, iv) PCC, DMF, r.t., 30 h, 67%; v) CH_2N_2, Et_2O, r.t., 99%; vi) 2-(trimethylsilyl)ethanol, Ti(OEt)$_4$, 100 °C, 50 h, 93%; vii) O_3, CH_2Cl_2, -78 °C, 45 min *then* DMS, r.t., 7 h, 98%; viii) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4/MeCN, pH 7 phosphate buffer, r.t., 20 min, 67%; ix) AcOH/H_2O, 75 °C, 8 h, 96%; x) 2-chloro-1-methylppyridinium iodide, DMAP, MeCN, 0 °C to r.t., 13 h, 74%; xi) MOMCl, (*i*-Pr)$_2$NEt, THF, 50 °C, 15 h, 91%; xii) lithium *N*-isopropylcyclohexylamide, acetaldehyde, THF, -60 °C to -20 °C, 1.5 h, 85%; xiii) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 0 °C, 6 h; xiv) DBU, CH_2Cl_2, 4 °C, 15 h, 75% over two steps; xv) 3M aw. HCl, THF, r.t., 1 h, 90%; xvi) LiOH, H_2O_2. B) *Reagents and conditions (some details were not provided by the authors)*: i) $(EtO)_2POCl$, NEt_3, THF, 0 °C to r.t., 3 h *then* **587**, DMAP, *n*-BuLi, 0 °C to r.t., 8 h, 55%; ii) NH_4F, MeOH/H_2O, 60 °C, 6 h, 65%; iii), MsCl, NEt_3, CH_2Cl_2, r.t., 2 h *then* TBAF, MeCN, r.t., 2 h, 75%; iv) EtOH, reflux, 1.5 h *then* 1 M aq. HCl, THF, 40°C, 1 h, 67%.

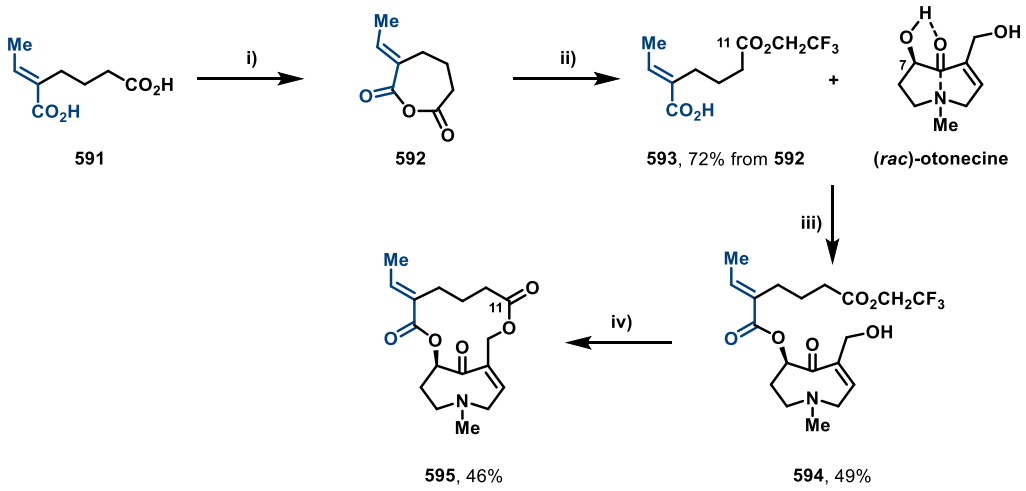
In 1996, Niwa, Yamada and co-workers published a synthesis of necic acid lactone **554b** en route to the retronecine-type macrocyclic diester, (+)-yamataimine (Scheme 136).[339] The relative stereochemistry of the necic acid of (+)-yamataimine (C12*S*, C13*R*) is diastereomeric to integerrinecic acid and senecic acid. Cyclopentanone **589** was readily prepared from (*R*)-pulegone in 49% yield over two steps. Methylation of cyclopentanone **589** was poorly diastereoselective (3:1 d.r.) providing cyclopentanone **553b** in 59% yield. The following Baeyer-Villager oxidation showed no regioselectivity resulting in the formation of a 1:1 ratio of lactones **554b** and **554a** (each in 40% yield). The C15-ethyl group of protected necic acid **590** was installed by the standard three step aldol condensation, employed in Niwa's previous synthesis of integerrinecic acid (Scheme 133A), followed by highly diastereoselective hydrogenation of the resulting exocyclic alkene. Methanolysis (K_2CO_3/methanol) of the resulting lactone (not shown) caused partial isomerisation of the C15-position, which, after further hydrolysis, provided protected necic acid **590** as a 2:1 mixture of C15-diastereomers (68% yield from **554b**). The remainder of the synthesis of (+)-yamataimine was accomplished using the strategy employed by Niwa, Yamada and co-workers in the synthesis of (-)-integerrimine (Scheme 133B).



Scheme 136: Niwa and Yamada's enantioselective synthesis of (+)-yamataimine. *Reagents and conditions (some details were not provided by the authors)*: i) Br_2, $NaHCO_3$, Et_2O, r.t., 40 °C *then* NaOMe, MeOH, reflux, 2.5 h, 77%; ii) O_3, DMS, MeOH, -78 °C, 63%; iii) MeI, K_2CO_3, acetone, r.t., 11 h, 59% of **553b**; iv) *m*-CPBA, Li_2CO_3, CH_2Cl_2, reflux, 4 d, 40% of **554b**; v) LDA, THF, -78 °C, 1 h *then* acetaldehyde, -30 °C, 2 h; vi) MsCl, pyridine, r.t., 2 h; vii) DBU, PhH, reflux, 2 h, 77% from **554b**; viii) 10% Pd/C, H_2, EtOAc, r.t., 16 h, 98%, single C15-diastereomer; ix) K_2CO_3, MeOH, r.t., 13 h *then* Ac_2O, DMSO, 40 °C, 24 h, 99%, 2:1 d.r.; x) 5 M aq. LiOH, THF/H_2O, r.t., 2 d, 91%; xi) DCC, CH_2Cl_2, r.t., 2 h; xii) (+)-retronecine, Bu_2SnO, Dean-Stark apparatus, PhH, reflux, 24 h *then* **590**, PhMe, r.t., 16 h, 81% over two steps; xiii) DCC, DMAP, CSA, $CHCl_3$, r.t., 5 d, 16%; xiv) $Ph_3C{\cdot}BF_4$, CH_2Cl_2, r.t., 16 h, 64%.

3.3.1.5 Niwa's model studies into the formation of otonecine-type macrocyclic diesters

The macrolactonisation strategies discussed up until this point have focussed on the synthesis of retronecine-type macrocyclic diesters, so it is unclear whether these methods will be applicable to the synthesis of otonecine-type macrocyclic diesters. In 1994, Niwa and co-workers published the only existing model studies into the macrolactonisation of (*rac*)-otonecine with a simple necic acid surrogate **591** (Scheme 137). The authors differentiated the two carboxylic acids of **591** by forming cyclic anhydride **592**, which was regioselectively opened by reaction with trifluoroethanol to give C11-monoester **593**. Unexpectedly, the secondary C7-alcohol of (*rac*)-otonecine underwent selective esterification in the presence of the primary C9-alcohol to form monoester **594**. The authors suggest that the secondary C7-alcohol was more reactive than the primary C9-alcohol due to a hydrogen bond with the highly polarised ketone (due to the N-C8 transannular interaction). Macrolactonisation of monoester **594** was achieved by transesterification in the presence of DMAP to form the model otonecine-type macrocyclic diester **595**.



Scheme 137: Yamada's synthesis of model otonecine-type pyrrolizidine alkaloid **595**. *Reagents and conditions (some details were not provided by the authors)*: i) DCC, CH_2Cl_2; ii) TFE, pyridine, 72% from **591**; iii) (*rac*)-otonecine, DCC, CSA, DMAP, $CHCl_3$, r.t., 1.5 h, ; iv) Bu_3SnOMe, DMAP, PhMe, reflux, 22 h, 46%.

3.3.2 Summary of the existing methods for the synthesis of C_{10} dicarboxylic necic acids and macrocyclic diesters

To summarise, several strategies for the synthesis of C_{10} dicarboxylic necic acids were disclosed in the period 1967 to 1996, but since then no new examples have been published. Most of these strategies suffer from either long step counts, inefficient or unselective transformations, or are not asymmetric, which renders them unsuitable in the current context. For example, the shortest route to any of the C_{10} dicarboxylic acids, Drewes and Emslie's five step synthesis of integerrinecic acid (Scheme 131), provides the necic acid as its racemate and requires the use of toxic sodium cyanide. By

comparison, the existing asymmetric syntheses require longer step counts (10 to 22 steps), which is perhaps a reflection of them being limited by the number of asymmetric methodologies available at the time. The shortest of these asymmetric syntheses, Niwa and Yamada's ten step synthesis of protected necic acid **590** from (*R*)-pulegone, contains poorly selective methylation and Baeyer-Villiger oxidation steps, which severely reduced the overall efficiency of the route. Additionally, the strategies described above are unsuitable for the divergent synthesis of diastereomeric C_{10} dicarboxylic necic acids.

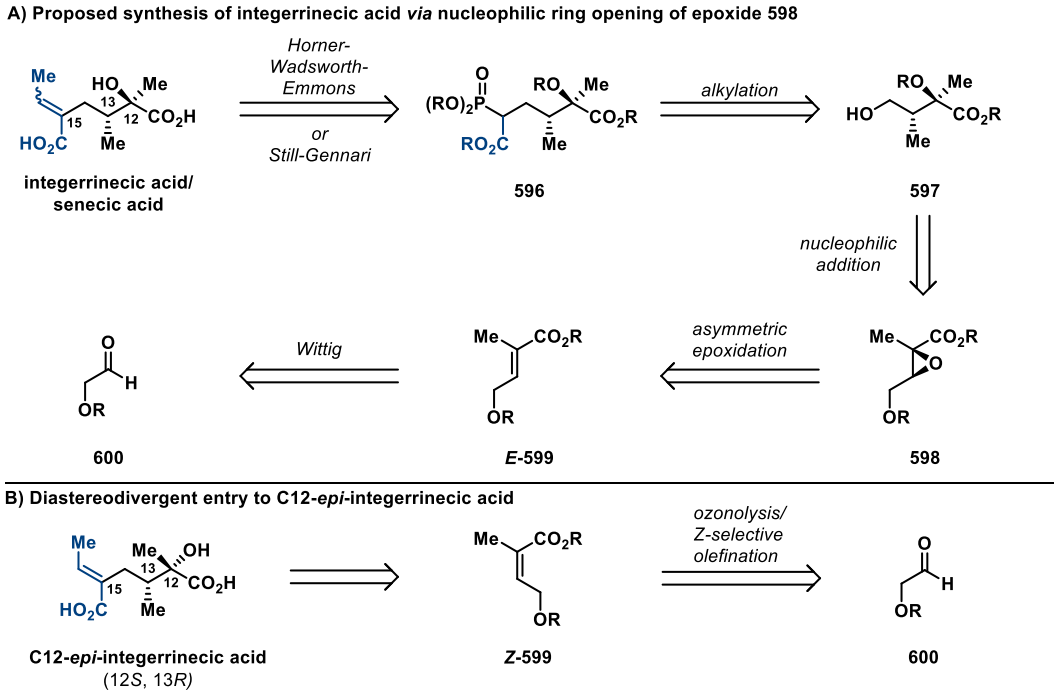
The existing macrocyclisation strategies require significant modifications and protection of the necic acid and necic base portions to facilitate coupling. This is illustrated in Narasaka's early synthesis of (*rac*)-integerrimine, where the necic acid coupling partner **(*rac*)-556** is prepared in nine steps from integerrinecic acid lactone **(*rac*)-555** and requires a further six steps to access the natural product (Scheme 132). Promisingly however, the only model studies towards the formation of an otonecine-type macrocyclic diester, Yamada's synthesis of model macrocyclic diester **595** (Scheme 137), proceeded in only four steps.

3.3.3 Development of an enantioselective synthesis of the C_{10} dicarboxylic necic acids

The considerations outlined in the previous section prompted attempts to develop a short and selective synthesis of the C_{10} dicarboxylic acids. The ideal synthesis would provide a highly selective entry to all the diastereomers shown in Figure 4 and be adaptable to the synthesis of some of the higher functionalised necic acids (see Figure 4).

3.3.3.1 First-generation retrosynthesis of (*rac*)-integerrinecic acid

Retrosynthetic analysis of integerrinecic acid identified primary alcohol **597** as a potential key intermediate, which could be advanced to the target molecule by olefination of phosphonoacetate **596** (Scheme 138A). This strategy was appealing because both C15 alkene isomers (*E* or *Z*) could potentially be accessed stereoselectively by appropriate choice of olefination conditions (e.g. Horner-Wadsworth-Emmons[340] or Still-Gennari[341]). The C12,C13-vicinal stereocentres of primary alcohol **597** might be formed by nucleophilic ring opening of epoxide **598**, which in turn is accessed *via* *E*-α,β-unsaturated ester ***E*-599**. The asymmetric synthesis would require an enantioselective epoxidation of α,β-unsaturated ester ***E*-599**, which might be achieved by several protocols.[342-344] Finally, synthesis of the C12-diastereomers of integerrinecic acid and senecic acid would be achieved from Z-α,β-unsaturated ester ***Z*-599** by an otherwise identical route (Scheme 138B).

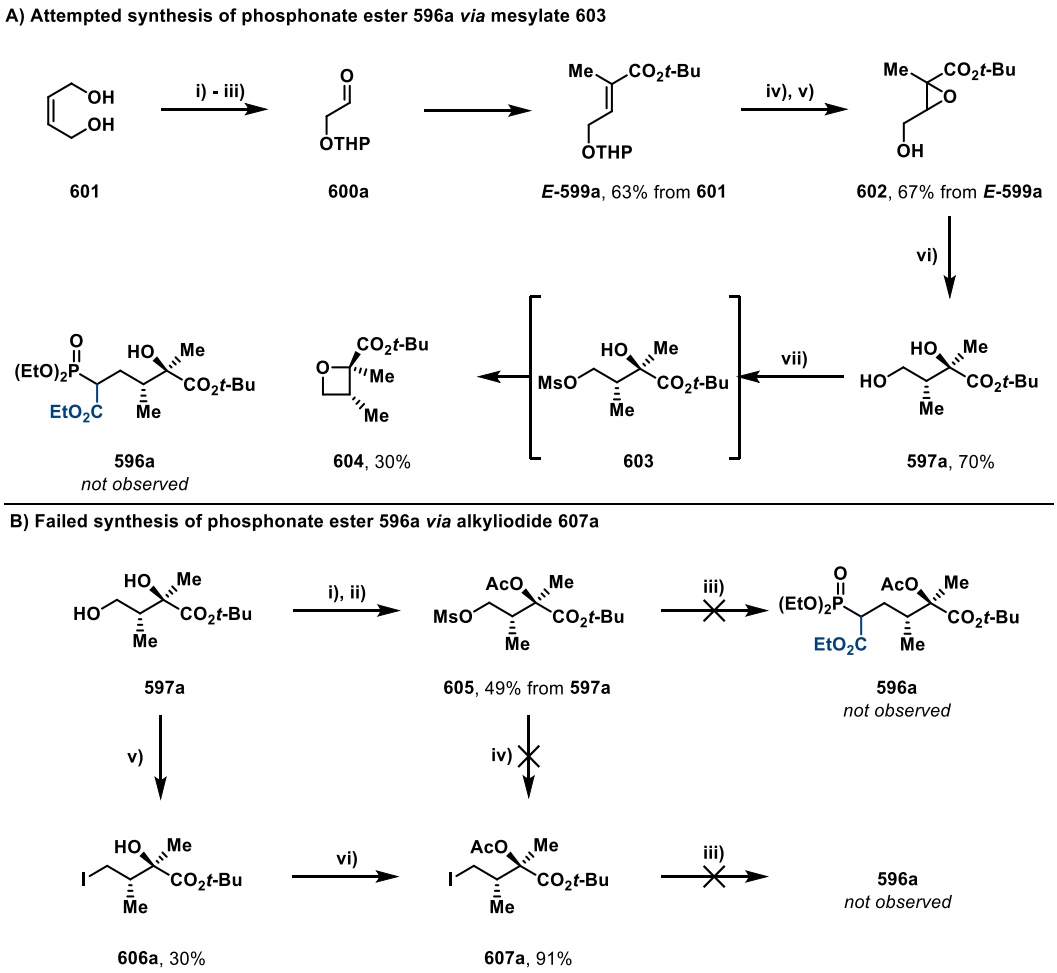


Scheme 138

Initial synthetic studies were directed towards the synthesis of (*rac*)-integerrinecic acid. Following a literature procedure, diol **601** was protected as the *bis*-THP acetal in quantitative yield, before undergoing ozonolysis to give aldehyde **600a**, which was immediately subjected to Wittig olefination to afford *E*-α,β-unsaturated ester ***E*-599a** in 64% yield (Scheme 139A).[345] At this point, epoxidation of α,β-unsaturated ester ***E*-599a** was carried out in a non-enantioselective manner, by treatment with *m*-CPBA, which gave epoxide **602** in 67% yield after THP-deprotection. Alcohol-directed nucleophilic ring opening of epoxide **602** with MeMgBr and copper(I) iodide proceeded rapidly to form diol **597a** in 70% yield. This robust sequence provided substantial quantities of the key intermediate, primary alcohol **597a**, for investigations into the olefination step.

In order to install the phosphonoacetate moiety, diol **597a** was reacted with methanesulfonyl chloride and the resulting mesylate was treated with deprotonated triethyl phosphonoacetate (TEPA). Unfortunately, the reaction did not form diester **596a**, but resulted in intramolecular nucleophilic substitution of the mesylate by the tertiary alcohol, forming oxirane **604** 30% yield. To avoid this intramolecular etherification, the tertiary alcohol of mesylate **603** was acetylated, but subsequent reaction with TEPA also failed (Scheme 139B). Therefore, alkyliodide **606a** was targeted in the hope that the iodide would undergo successful intermolecular substitution. Whereas reaction of mesylate **605** with sodium iodide caused degradation, alkyliodide **607a** could be accessed by an alternative route involving iodination (30% yield) and acetylation (90% yield) of diol **597a**. Unfortunately, alkyliodide **607a** also failed to form diester **596a** when reacted with deprotonated TEPA. At this point, the retrosynthetic analysis in Scheme 138 was re-evaluated because of the difficulties in synthesising

diester **596a** and because the current proposal was not significantly more step economical (>10 steps to access integerrinecic acid) than previous reports.

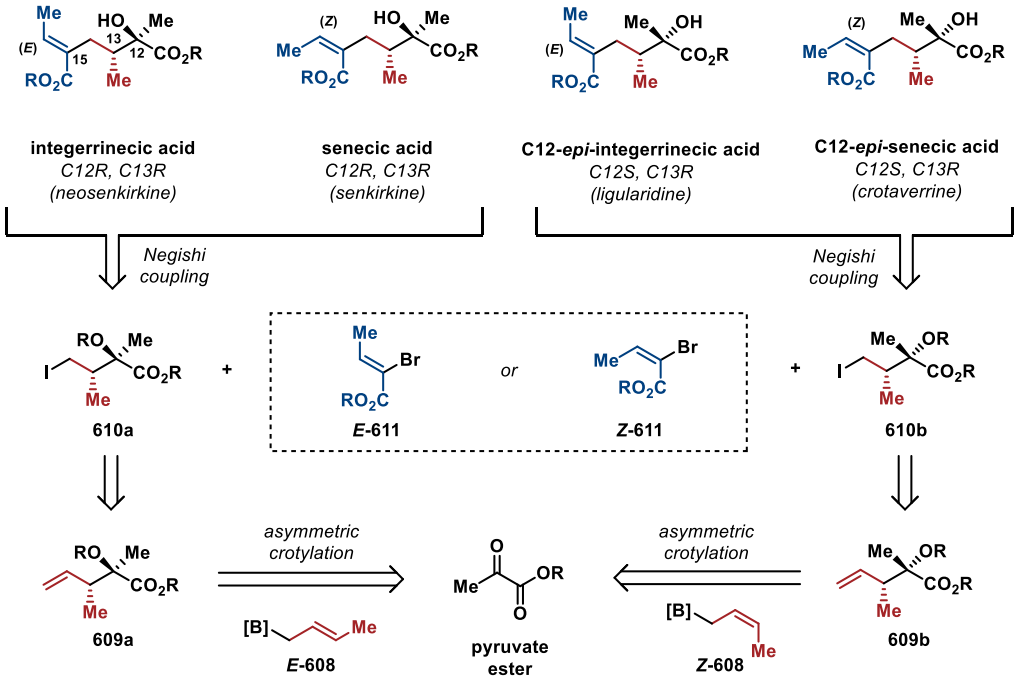


Scheme 139: A) *Reagents and conditions*: i) 3,4-dihydropyran, *p*-TSA, CH_2Cl_2, r.t., 1.5 h, 98%; ii) O_3, CH_2Cl_2, -78 °C, 5 h *then* PPh_3, r.t., 2 h; iii) *t*-butyl 2-(triphenylphosphoranylidene)propionate, CH_2Cl_2/PhMe, r.t., 16 h, 64% from **601**; iv) *m*-CPBA, CH_2Cl_2, r.t., 48 h; v) *p*-TSA, MeOH, r.t., 4 h, 67% from ***E*-599a**; vi) MeMgBr, CuI, THF, -15 °C, 15 min, 70%; vii) MsCl, NEt_3, CH_2Cl_2, 0 °C, 15 min *then* TEPA, NaH, THF, 0 °C – reflux, 3 h, 30%. B) *Reagents and conditions*: i) MsCl, NEt_3, CH_2Cl_2, 0 °C, 15 min; ii) Ac_2O, DMAP, pyridine, r.t., 16 h, 49%; iii) TEPA, NaH, THF, 50 °C; iv) NaI, acetone, 50 °C; v) PPh_3, I_2, imidazole, CH_2Cl_2, 0 °C to r.t., 16 h, 30%; vi) Ac_2O, DMAP, pyridine, r.t., 6 h, 91%.

3.3.3.2 Second-generation retrosynthesis of integerrinecic acid and its diastereomers

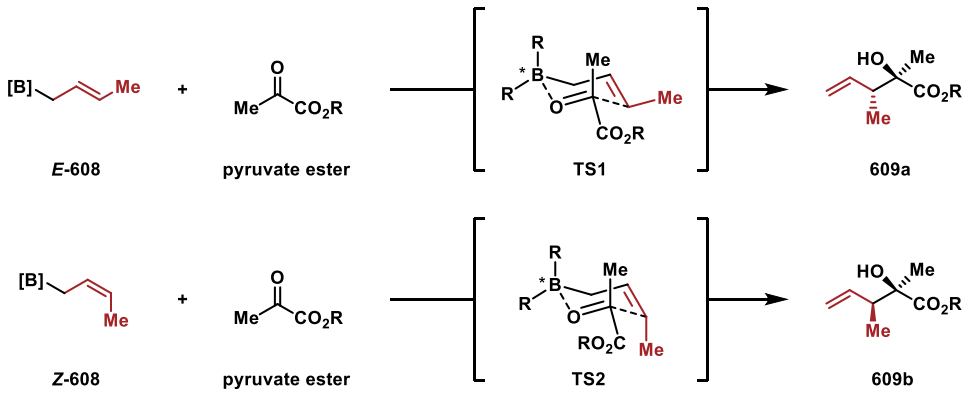
The second-generation retrosynthetic analysis of integerrinecic acid is shown in Scheme 140. The retrosynthesis relies on two key transformations, the asymmetric crotylation of a pyruvate ester to form the C12,C13-vicinal stereocentres, and a Negishi cross-coupling to attach the exocyclic alkene portion. The proposed strategy is highly modular, such that the four necic acid diastereomers (integerrinecic acid, senecic acid, C12-*epi*-integerrinecic acid and C12-*epi*-senecic acid) might be

accessed in a divergent manner by appropriate choice of crotylboron reagent (i.e. ***E*-608** or ***Z*-608**) and Negishi cross-coupling electrophile (i.e. ***E*-611** or ***Z*-611**).



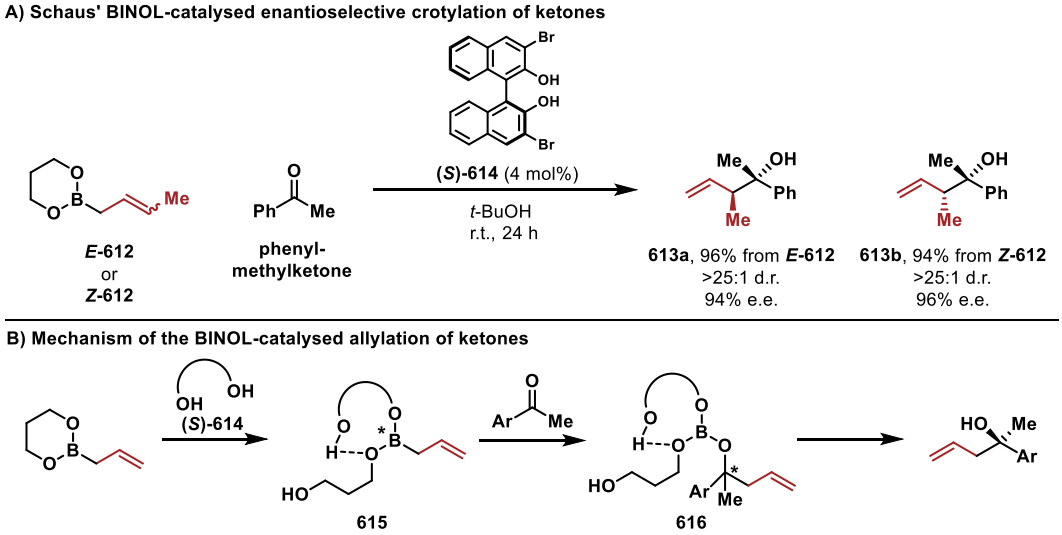
Scheme 140: Asymmetric crotylation and Negishi cross-coupling towards the C_{10} dicarboxylic necic acids.

The proposed synthesis begins with the diastereoselective and enantioselective crotylation of a pyruvate ester to form alkenes **609a** or **609b**. Asymmetric allylation of aldehydes and ketones is a powerful method for the formation of chiral secondary and tertiary alcohols.[346-347] Numerous allyl-metal reagents have been reported to undergo such a reaction, and, among these, allylboron reagents have been particularly successful. However, whereas the asymmetric allylation of aldehydes is highly developed, the asymmetric allylation of ketones remains challenging and is typically limited to activated ketones.[348] Nevertheless, this strategy was appealing because both diastereomers of the crotylation product might be accessed depending on whether the *E*- or *Z*-crotylboron reagent is used. For example, *E*-crotylboron reagent ***E*-608** would react with pyruvate ester *via* six-membered chair transition state **TS1**. Here the vinyl methyl moiety of boron reagent is positioned in a *pseudo*-equatorial position and the ester moiety of pyruvate ester is positioned in a *pseudo*-equatorial position such that (*R*,*R*)-alkene **609a** is formed (Scheme 141). Alternatively, by employing Z-crotylboronic ester ***Z*-608**, the methyl moiety of boron reagent is positioned in a *pseudo*-axial orientation in the corresponding transition state **TS2**, resulting in the formation of (*R*,*S*)-alkene **609b**. Alkenes **609a** and **609b**, resulting from the crotylation reaction, might be advanced to alkyliodides **610a** and **610b** by standard functional group transformations (Scheme 140). Then, Negishi cross-coupling, between an alkyl zinc reagent derived from alkyliodides **610a** and **610b**, and electrophiles ***E*-611** or **Z-611s** would rapidly form the desired necic acid in a protected form.



Scheme 141: Asymmetric and diastereoselective crotylation of a pyruvate ester.

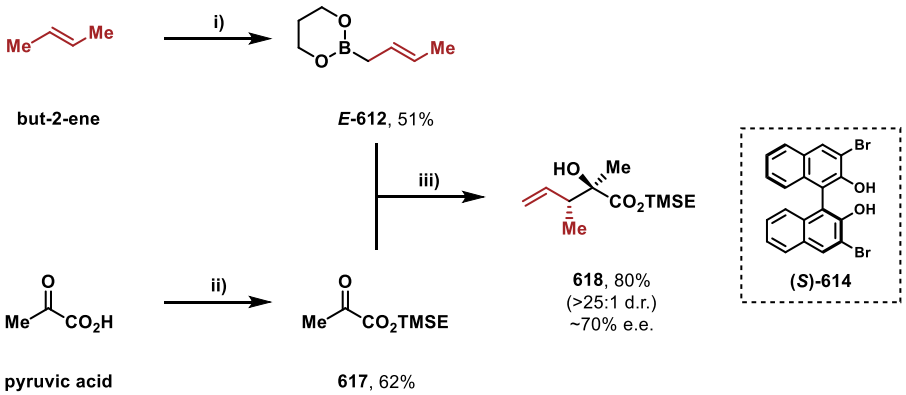
The viability of the second-generation strategy was investigated by targeting integerrinecic acid. Initially, a literature survey was conducted to identify suitable conditions for the asymmetric crotylation of pyruvate esters, but no examples existed at the time. However, a report by Schaus and co-workers described the highly enantioselective crotylation of phenylmethylketone to form either alkene **613a** or **613b** depending on the crotylboron reagent used (i.e. ***E*-612** or ***Z*-612**) (Scheme 142A).[348-349] This methodology employs BINOL-derived catalyst **(*S*)-614**, which is proposed to undergo ligand exchange with an allylboronic ester to form active chiral boronate species **615** (Scheme 142B). Upon allylboration of an aryl ketone, BINOL-derived catalyst **(*S*)-614** is regenerated from resulting species **616** by ligand exchange with *t*-BuOH.



Scheme 142

Schaus' conditions were chosen to investigate the crotylation of pyruvate ester **617** by *E*-crotylboronic ester ***E*-612** (Scheme 143). The TMSE-ester of **617** was chosen to provide an orthogonal mode of deprotection (i.e. TBAF) at a later stage in the synthesis where other ester functionalities might be present. *E*-Crotylboronic ester ***E*-612** was prepared in 51% yield by a known procedure involving

deprotonation of but-2-ene with Schlosser's base and borylation of the resulting lithiated species.[349] Pyruvate ester **617** was prepared by EDCI coupling of pyruvic acid with 2-trimethylsilylethanol in 62% yield. Gratifyingly, under Schaus' BINOL-catalysed conditions, pyruvate ester **617** underwent rapid crotylation with *E*-crotylboronic ester ***E*-612** to provide alkene **618** in 80% yield, as a single diastereomer and in a promising 70% e.e.. The relative stereochemistry of alkene **618** was confirmed by comparison of the ^{13}C chemical shifts with a literature compound (*Further details are available in the Experimental Section 4.5*). It is important to note that these results are entirely unoptimised. Further improvements to the enantioselectivity of the reaction might be achieved by lowering the reaction temperature to minimise background non-enantioselective crotylation reactions.

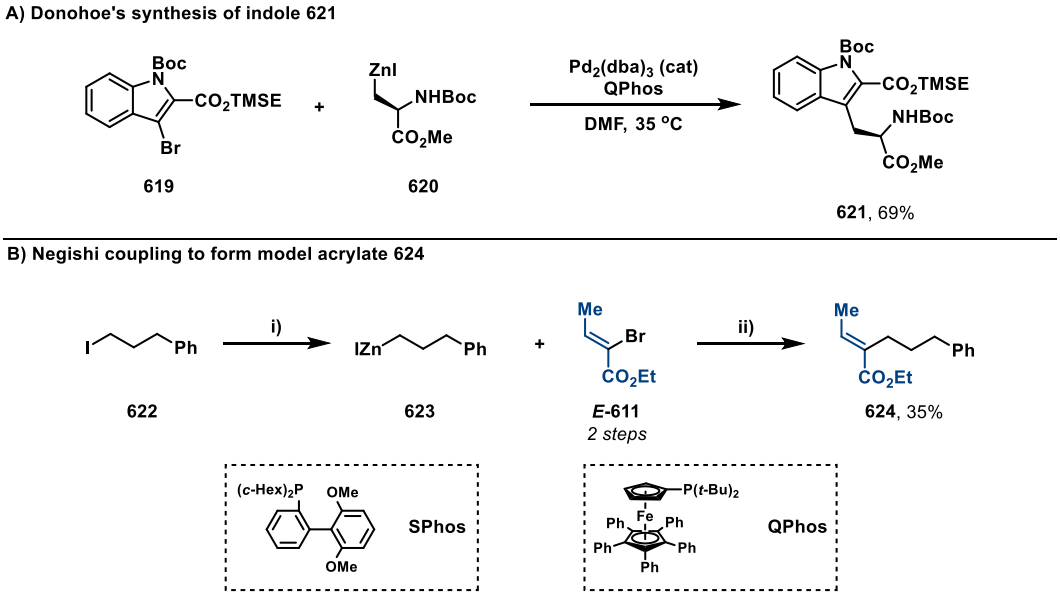


Scheme 143: Application of Schaus' conditions to the asymmetric crotylation of pyruvate ester **617**. *Reagents and conditions*: i) KO*t*-Bu, *n*-BuLi, THF, -78 °C to -52 °C, 15 min *then* B(O*i*-Pr)$_3$, -78 °C, 3 h *then* 3 M aq. HCl *then* 1,3-propanediol, 4 Å MS, r.t., 16 h, 51%; ii) 2-(trimethylsilyl)ethanol, EDCI, DMAP, CH_2Cl_2, r.t., 16 h, 62%; iii) **(*S*)-614**, *t*-BuOH, PhMe, r.t., 3 h, 80%, >25:1 d.r., ~70% e.e..

Having identified promising conditions for the crotylation reaction, attention was turned to the proposed Negishi cross-coupling. Negishi cross-couplings are a mild method for the coupling of sp^3 and sp^2-hybridised carbon-centres in the presence of various sensitive functional groups, which has resulted in it having been employed extensively in the total synthesis of complex molecules.[350-351] The functional group tolerance of the Negishi cross-coupling is demonstrated by Donohoe and co-workers in the synthesis of dehydromicrosclerodermin B (Scheme 144A).[352] Here, Negishi cross-coupling of alkylzinc species **620** (formed from the corresponding alkyliodide) with 2-bromoindole **619** was carried out in the presence of an acidic N-H bond and TMSE-ester, to form product **621** in 69% yield. A literature survey did not find any examples of α-bromoacrylates being used as electrophiles in Negishi cross-couplings, so due to the structural similarities between the reagents in Scheme 144A and the proposed Negishi cross-coupling described in Scheme 140, investigations began with the conditions reported by Donohoe.

Exploratory studies into the proposed Negishi cross-coupling were carried out with model alkyliodide **622** and α-bromoacrylate ***E*-611** (Scheme 144B). According to Donohoe's conditions,

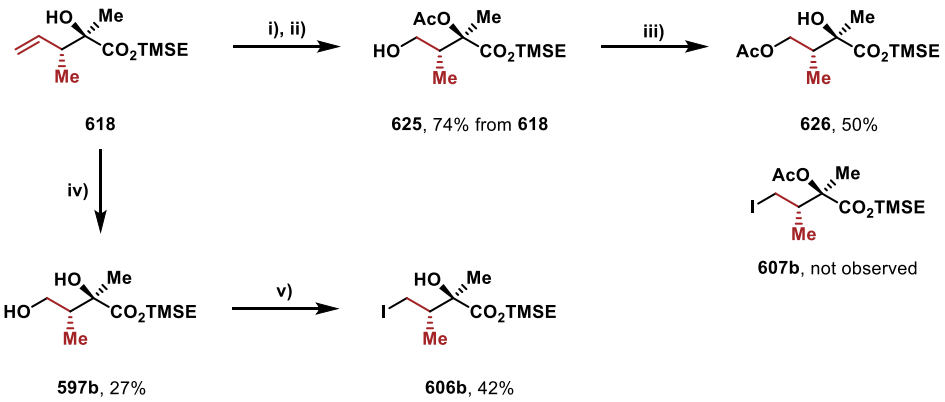
alkylzinc reagent **623** was formed from alkyliodide **622** by reaction with activated zinc. Alkylzinc reagent **622** was then added to α-bromoacrylate ***E*-611** in the presence of catalytic Pd_2dba_3 and SPhos, which provided cross-coupling product **624** in 35% yield. Note, due to availability issues, the suboptimal ligand, SPhos, was used in this reaction instead of QPhos. Although further optimisation is required, the formation of cross-coupling product **624** suggests that the proposed coupling of complex alkyliodide **610** and α-bromoacrylate ***E*-611** might be achieved under these conditions.



Scheme 144: A) *Reagents and conditions*: i) Zn dust, TMSCl, dibromoethane, DMF, r.t., 2 h; ii) $Pd_2(dba)_3$, SPhos, DMF, 40 °C, 16 h, 35%.

Next a suitable alkyl iodide species was targeted in order to investigate the Negishi cross-coupling. Therefore, alcohol **618** was acetylated before undergoing reductive ozonolysis to form alcohol **625** in 86% yield (Scheme 145). When subjected to standard iodination conditions, the acetate of alcohol **625** migrated to the primary alcohol resulting in the formation of primary acetate **626** and none of the desired iodide **607b**. Therefore, an alternative order of transformations was investigated. Reductive ozonolysis of alkene **618** formed diol **597b** albeit in a disappointing 27% yield. Iodination of diol **597b** successfully formed iodide **606b** but in only 47% yield. Despite the poor yields, iodide **606b** is a viable substrate for investigating the proposed Negishi coupling.

No further investigations were carried out towards the synthesis of integerrinecic acid due to time constraints. It is clear from the immediately high yielding and selective formation of alkene **618** by crotylation of pyruvic ester **617**, subsequent synthesis of iodide **606b** and promising model studies into the sp^2-sp^3 Negishi cross-coupling that this novel strategy shows great promise in the synthesis of integerrinecic acid and its natural diastereomers.



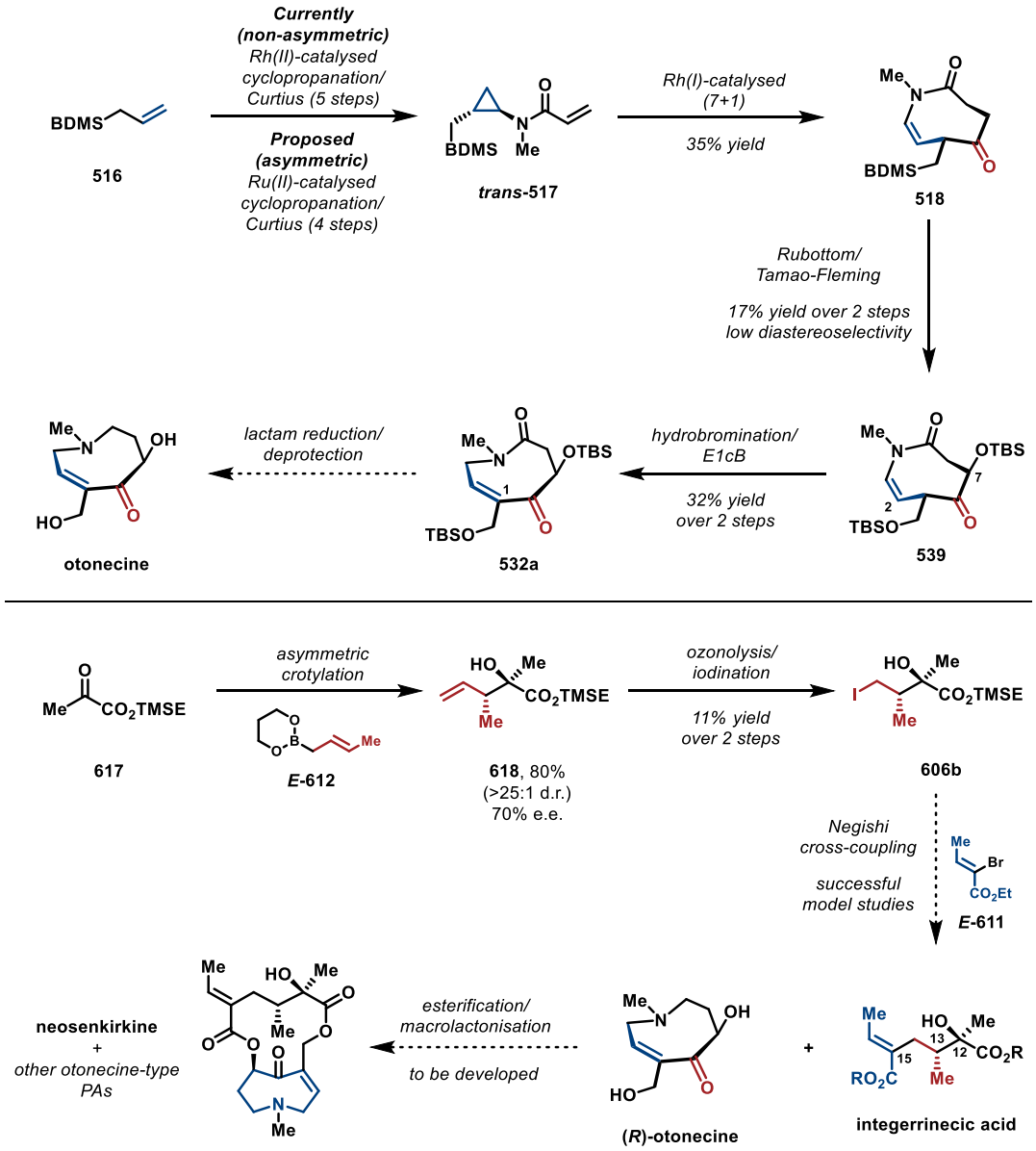
Scheme 145: Synthesis of alkyliodide **606b** from alkene **618**. *Reagents and conditions*: i) Ac_2O, DMAP, pyridine, r.t., 6 h, 86%; ii) O_3, CH_2Cl_2/MeOH, -78 °C *then* $NaBH_4$, 0 °C, 30 min, 86%; iii) PPh_3, I_2, imidazole, CH_2Cl_2, 0 °C to r.t., 16 h, 50%; iv) O_3, CH_2Cl_2/MeOH, -78 °C *then* $NaBH_4$, 0 °C, 3 h, 27%; v) PPh_3, I_2, imidazole, CH_2Cl_2, 0 °C to r.t., 16 h, 42%.

3.3 Summary and conclusions from the studies in Chapter 3

Significant progress has been made towards the total synthesis of otonecine using the (7+1) carbonylative cycloaddition of cyclopropylacrylamides developed at Bristol. Cyclopropylacrylamide ***trans*-517** was identified as the optimal substrate for the (7+1) carbonylative cycloaddition, which was prepared by a robust five step sequence from allylsilane **516**. The current synthesis of cyclopropylacrylamide ***trans*-517** is not asymmetric, but strong literature precedent suggests that it may be prepared rapidly in an enantioenriched form. The existing conditions for the Rh(I)-catalysed (7+1) carbonylative cycloaddition were not suitable for the current application, so these were reoptimised. This led to the identification of beneficial additives and an alternative reaction set-up, which dramatically increased the efficiency of the (7+1) carbonylative cycloaddition and allowed access to suitable quantities of azocane **518** for further studies.

Extensive investigations into the four post-cycloaddition transformations provided suitable conditions for three of these and identified a viable sequence for these to be carried out. Firstly, azocane **518** underwent a two step Rubottom oxidation to install the C7-alcohol of otonecine. This was achieved in good yield, but further development is required to improve the diastereoselectivity of this reaction. Perhaps the greatest challenge encountered in this project was the incorporation of the C9-alcohol. Several methods were investigated, but Tamao-Fleming oxidation of the C9-silane proved to be successful, albeit in low yield under the current conditions. The alkene isomerisation from the C2-position (as in **539**) to the C1-position (as in **532a**) was another challenging transformation, which was achieved by a two step kinetic method employing a one-pot hydrobromination of the enelactam moiety. Unfortunately, the penultimate lactam reduction of lactam **532a** failed to form bis-TBS protected otonecine, instead forming an unassigned side-product under a variety of chemoselective reduction

conditions. Future efforts should aim to understand why this side-product is being formed, which might provide a solution to this final transformation.



Scheme 146: Current progress towards the total synthesis of otonecine and the otonecine-type pyrrolizidine alkaloids.

In parallel studies towards the synthesis of the C_{10} dicarboxylic necic acids, a potentially short and divergent synthesis has been designed. The asymmetric crotylation of pyruvate ester **617** promises to provide a highly efficient and diastereodivergent entry to alkene **618**, which contains the C12,C13-vicinal stereocentres of the necic acids. Model studies have identified conditions for the Negishi coupling of a simple alkyl iodide with α-bromoacrylate ***E*-611**, which might be applicable to the cross-coupling shown in Scheme 146.

Completion of the asymmetric synthesis of (*R*)-otonecine and the C_{10} dicarboxylic necic acids would set the stage for the first total synthesis of an otonecine-type PA, such as neosenkirkine. Model studies reported by Niwa and co-workers suggest that the union of (*R*)-otonecine and a necic acid might be achieved with relative efficiency.

Chapter 4 – Experimental

General Experimental Details. Starting materials sourced from commercial suppliers were used as received unless otherwise stated. Dry solvents, where necessary, were obtained by distillation using standard procedures or by passage through a column of anhydrous alumina using equipment from Anhydrous Engineering based on the Grubb's design.[353] The removal of solvents *in vacuo* was achieved using both a Büchi rotary evaporator (bath temperatures up to 40 °C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate, and a high vacuum line at room temperature. Reactions requiring anhydrous conditions were run under an atmosphere of dry nitrogen or argon; glassware was either flame dried immediately prior to use or placed in an oven (200 °C) for at least 2 h and allowed to cool either in a desiccator or under an atmosphere of nitrogen or argon; liquid reagents, solutions or solvents were added *via* syringe through rubber septa. Commercially available Merck Kieselgel $60F_{254}$ aluminium backed plates were used for TLC analysis. Visualisation was achieved by either UV fluorescence or basic $KMnO_4$ solution and heat. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40-63 μm, 230-400 mesh). The crude material was applied to the column as a solution in the corresponding solvent system, CH_2Cl_2, or by pre-adsorption onto silica, as appropriate. Melting points were determined using a Reichert melting point table and temperature controller and are uncorrected. Infra-red spectra were recorded in the range 4000-600 cm^{-1} on a Perkin Elmer Spectrum either as neat films or solids compressed onto a diamond window. Abbreviations used are: w (weak), m (medium) or s (strong). NMR spectra were recorded using either a Varian 400 MHz or JOEL ECS 400 MHz spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm), coupling constants (*J*) are given in Hz to the nearest 0.5 Hz. Other abbreviations used are s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). ^1H and ^{13}C NMR spectra were referenced to the appropriate residual solvent peak. Assignments of ^1H NMR and ^{13}C NMR signals were made, where possible, using COSY, DEPT[135], HSQC, HMBC and NOE experiments. Where mixtures of products (*e.g.* diastereomers, regioisomers or 8 vs 9) have been isolated together, they have been characterised separately where possible. *Numbering systems for NMR signal assignments are specified on the structure and are not related to those used for the compound names*. Mass spectra were determined by the University of Bristol mass spectrometry service by either electron impact (EI^+) or chemical ionisation (CI^+) using a Fisons VG Analytical Autospec spectrometer, or by electrospray ionisation (ESI^+) using a Brüker Daltonics Apex IV spectrometer. Chiral SFC was performed using the racemate as a standard on an Agilent 1290 Infinity system equipped with a quaternary pump, diode array detector and column thermostat under the conditions specified in each case.

4.1 General Procedures

General procedure A for the formation of ureas from cyclopropylamines

To a solution of amine (110 mol%) and NEt_3 (200 mol%) in CH_2Cl_2 (0.3 M) at 0 °C was added the specified isocyanate (100 mol%). The reaction mixture was warmed to room temperature and stirred for 16 h. The solution was diluted with CH_2Cl_2 (3 mL/mmol) and washed with water (5 mL/mmol), 1 M aq. HCl (5 mL/mmol), sat. aq. $NaHCO_3$ (5 mL/mmol) and brine (5 mL/mmol). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified by FCC, under the conditions noted, to afford the title compound.

General procedure B for the carbonylative cyclisation of cyclopropane-based substrates

An oven dried reaction tube fitted with a magnetic stirrer was charged with benzoic acid (15 mol%), the specified Rh(I)-catalyst (3.5–10 mol%), PPh_3 (twice the number of moles of Rh(I)-catalyst) and cyclopropylurea (100 mol%). The tube was fitted with a rubber septum and purged with argon. Argon sparged anhydrous 1,2-DCB (0.2 M) was added *via* syringe before the solution was aged the solution was aged for *ca.* 5 minutes. The reaction tube was purged with CO (balloon) for 20 minutes then the reaction mixture was sparged for 10 seconds. The reaction was heated at the specified temperature (90–100 °C) under CO (balloon) until complete consumption of the starting material was observed by TLC (23–92 h). The reaction mixture was cooled to room temperature, concentrated *in vacuo* and purified by FCC, under the conditions noted, to afford the target heterocycle.

General Procedure C for the hydrolysis of cyclopropyl esters to form cyclopropyl carboxylic acids

To a stirring solution of the ester (100 mol%) in MeOH (0.5 M) was added 4 M aq. NaOH (500 mol%). The reaction was stirred at the specified temperature for the specified time. MeOH was removed *in vacuo* and the aqueous layer was diluted with water (5 mL/mmol) before being acidified to pH ~1 with conc. HCl. The aqueous layer was extracted with Et_2O (3 × 5 mL/mmol), and the combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the title compound.

General Procedure D for the Curtius rearrangement of cyclopropylcarboxylic acids to form Boc-protected cyclopropylamines

To a stirring solution of carboxylic acid (100 mol%) in dry *t*-BuOH (1 M) was added NEt_3 (110 mol%) then diphenylphosphoryl azide (110 mol%) after 10 minutes. The reaction was stirred at room temperature for 30 minutes, heated at 80 °C for the specified time and then concentrated *in vacuo*. The resulting residue was dissolved in sat. aq. $NaHCO_3$ (5 mL/mmol) and extracted with Et_2O (3 × 5 mL/mmol). The combined organics were washed with brine (5 mL/mmol), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC, under the conditions noted, provided the title compound.

General procedure E for the one-pot Boc-deprotection/reductive amination of Boc-protected cyclopropylamines

To a solution of the specified Boc-protected cyclopropylamine (100 mol%) in CH_2Cl_2 (1 M) was added trifluoroacetic acid (1000 mol%), and the reaction was stirred at room temperature for 30 minutes before being concentrated *in vacuo*. The resulting amine·TFA salt was dissolved in water (5 mL/mmol), and the aqueous phase was washed with CH_2Cl_2 (5 mL/mmol). The aqueous phase was basified to pH ~12 by the addition of 2 M aq. NaOH and extracted with CH_2Cl_2 (3 × 3 mL/mmol). The combined organics were dried over Na_2SO_4, concentrated *in vacuo* and the residue was dissolved in MeOH (0.5 M). $NaHCO_3$ (400 mol%) and benzaldehyde (95 mol%) were added, and the solution was heated at reflux for 24 h. The reaction mixture was cooled to 0 °C and $NaBH_4$ (125 mol%) was added portion-wise over 10 minutes. The reaction was warmed to room temperature, stirred for 18 h and then concentrated *in vacuo*. Sat. aq. $NaHCO_3$ (10 mL/mmol) and CH_2Cl_2 (5 mL/mmol) were added, the layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 × 5 mL/mmol). The combined organics were washed with brine (5 mL/mmol), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC, under the conditions noted, provided the title compound.

General procedure F for the one-pot Boc-deprotection/urea formation of Boc-protected cyclopropylamines

To a solution of Boc-protected cyclopropylamine (100 mol%) in CH_2Cl_2 (1 M) was added trifluoroacetic acid (1000 mol%), and the reaction was stirred at room temperature for 30 minutes before being concentrate *in vacuo*. The resulting trifluoroacetate salt and NEt_3 (250 mol%) were dissolved in CH_2Cl_2 (0.3 M) before the addition of benzyl isocyanate (95 mol%). The reaction was stirred at room temperature for 2 h before being diluted with CH_2Cl_2 (5 mL/mmol). The solution was washed with water (5 mL/mmol), 1 M aq. HCl (5 mL/mmol), sat. aq. $NaHCO_3$ (5 mL/mmol) and brine (5 mL/mmol), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC, under the conditions noted, provided the target compound.

General Procedure G for the *N*-methylation of Boc-protected amines

To a stirring suspension of NaH (equivalents specified, 60% dispersion in mineral oil) in anhydrous THF (0.3 M) at 0 °C was added a solution of Boc-protected amine (100 mol%) in dry THF (2 M). The resulting suspension was stirred at 0 °C for 30 minutes before being warmed to room temperature. MeI (equivalents specified) was then added dropwise over 5 minutes and the reaction was stirred at the specified temperature for the specified time, or until complete by TLC. The completed reaction mixture was quenched with H_2O (5 mL/mmol) and extracted with Et_2O (3 × 5 mL/mmol). The combined organics were washed with brine (5 mL/mmol), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC, under the conditions noted, yielded the desired *N*-methyl carbamate.

General Procedure H for the one pot Boc-deprotection/acrylamide formation

To a stirring solution of Boc-protected amine (100 mol%), in CH_2Cl_2 (1 M), was added trifluoroacetic acid (1000 mol%). The reaction was stirred at room temperature until complete by TLC (typically 15 minutes) before being concentrated *in vacuo* (residual trifluoroacetic acid was removed by redissolving the resulting residue in CH_2Cl_2 and concentrating *in vacuo* three times). The resulting trifluoroacetic acid salt was dissolved in acetone (0.4 M) and H_2O (1.7 M), and K_2CO_3 (300 mol%) was added. The reaction mixture was cooled to 0 °C, and acryloyl chloride (200 mol%) was added dropwise by syringe over 5 minutes. The reaction mixture was stirred at room temperature for 16 h before being concentrated *in vacuo*, dissolved in H_2O (5 mL/mmol), and extracted with CH_2Cl_2 (3 × 5 mL/mmol). The combined organics were washed with brine (5 mL/mmol), sat. aq. $NaHCO_3$ (2 × 5 mL/mmol) and dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC under the conditions noted yielded the desired acrylamide. *Note: The resulting acrylamides have been observed to polymerise and were therefore stored in the freezer as a solution in Et_2O.*

General Procedure I for the (7+1) carbonylative cycloaddition of cyclopropylacrylamides in a Schlenk tube

To a flame-dried Schlenk tube equipped with a magnetic stirrer bar and Young's tap adapter, was added the Rh(I)-catalyst (equivalents specified), ligand (equivalents specified) and additive (equivalents specified). The Schlenk tube was attached to a Schlenk line and CO cylinder *via* a three-way adapter. The flask was evacuated and refilled with nitrogen twice before being evacuated and refilled with CO (approximately 2 atm pressure). Whilst under a positive pressure of CO (approximately 2 atm), the Youngs tap was replaced with a rubber septum, which was pierced with a needle attached to a bubbler in order to monitor the pressure of CO. Meanwhile, acrylamide (100 mol%) was dissolved in argon sparged, anhydrous benzonitrile (0.1 M) in a flame-dried flask before being transferred to the Schlenk flask by syringe. The rubber septum was replaced with a Youngs tap and the Schlenk tube was sealed. The Schlenk tube was shaken to incorporate CO into the reaction mixture then heated at the specified temperature for the specified time. The Schlenk tube was then cooled to room temperature, and the reaction mixture was transferred to a separate flask before being concentrated *in vacuo*. The method of purification is specified.

General Procedure J for the hydrobromination of enelactams

Enelactam (100 mol%) in anhydrous CH_2Cl_2 (0.1 M) was transferred to a flame-dried flask containing $NaHCO_3$ (300 mol%) under an atmosphere of argon. The resulting suspension was cooled to 0 °C. Bromine (~110 mol%) was added dropwise by syringe until a red/brown colour persists for longer than 10 seconds. Immediately afterwards, excess bromine was consumed by the dropwise addition of 2,3-dimethylbut-2-ene (1 M THF) until the solution became colourless. THF (0.2 M) was added, followed by $NaBH_3CN$ (150 mol%). The suspension was warmed to room temperature and stirred for

30 minutes before being quenched with sat. aq. NH_4Cl (5 mL/mmol). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL/mmol) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC, under the specified conditions, provided the title compound.

General Procedure K for the E1cB elimination from β-bromoketones

The β-bromoketone (100 mol%) was dissolved in CH_2Cl_2 (0.1 M) and base (specified equivalents) was added. The reaction was followed closely by TLC to minimise isomerisation of the desired α,β-unsaturated ketone. The reaction was quenched by the addition of sat. aq. NH_4Cl (5 mL/mmol), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL/mmol). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC provided the title compound.

General Procedure L for the synthesis of oximes from ketones

Oxime HCl salt (equivalents specified) and NaOAc (equivalents specified) were added to a stirring solution of ketone (100 mol%) in EtOH (0.1 M). The reaction was run for the specified time at the specified temperature before being concentrated *in vacuo*. The crude mixture was dissolved in sat. aq. $NaHCO_3$ (5 mL/mmol) and extracted with Et_2O (5 mL/mmol). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound which was typically pure enough for the following step.

General Procedure M for the synthesis of carboxylic acid containing oximes from ketones

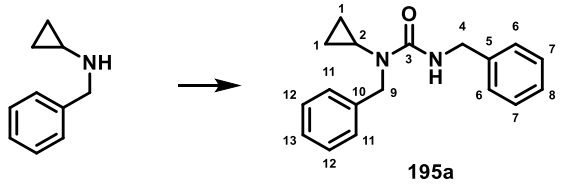
Oxime HCl salt (equivalents specified) and NaOAc (equivalents specified) were added to a stirring solution of ketone (100 mol%) in EtOH (0.1 M). The reaction was run for the specified time at the specified temperature before being concentrated *in vacuo*. The crude mixture was dissolved in Et_2O (5 mL/mmol) and extracted with aq. 10 wt% K_2CO_3 (3 × 2 mL/mmol). The combined aqueous layer was acidified to pH ~1 with conc. HCl and extracted with Et_2O (3 × 5 mL/mmol). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound, which was typically pure enough for the following step.

General Procedure N for the Pd(II)-catalysed β-acetoxylation of oximes

Oxime (100 mol%), $Pd(OAc)_2$ (equivalents specified) and $PhI(OAc)_2$ (equivalents specified) were dissolved in the specified solvent and heated at the specified temperature for the specified time. The completed reaction mixture was filtered through celite and concentrated *in vacuo*. The yield was determined by analysis of the ^1H NMR spectrum against 1,4-DNB as an internal standard. Further purification will be specified.

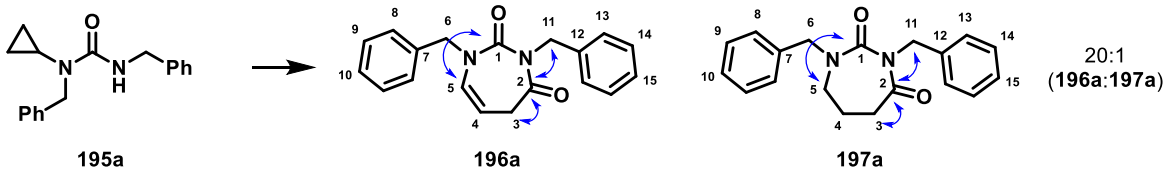
4.2 Experimental procedures for the studies in Section 2.1

1,3-Dibenzyl-1-cyclopropylurea (195a)



General procedure A: *N*-Benzylcyclopropanamine[354] (1.77 g, 11.0 mmol) and benzyl isocyanate (1.24 mL, 10.0 mmol) were employed. The crude mixture was purified by FCC (50% EtOAc/hexane) to yield the title compound **195a** (2.26 g, 81%) as a colourless solid; m.p. 80–82 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3369 (s), 1635 (s), 1504 (s), 1285 (m), 1230 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.21 (10H, m, 2 × C**6**-H, 2 × C**7**-H, C**8**-H, 2 × C**11**-H, 2 × C**12**-H and C**13**-H), 5.61 (1H, t, *J* = 5.5 Hz, NH), 4.58 (2H, s, C**9**-H_2), 4.50 (2H, d, *J* = 5.5 Hz, C**4**-H_2), 2.35 (1H, tt, *J* = 7.0, 4.0 Hz, C**2**-H), 0.78–0.74 (4H, m, C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1 (C**3**), 139.8 (C**5**), 139.1 (C**10**), 128.7, 128.5, 128.0, 127.5, 127.3, 127.0 (C**6**, C**7**, C**8**, C**11**, C**12** and C**13**), 50.6 (C**9**), 44.9 (C**4**), 27.8 (C**2**), 8.8 (C**1**); HRMS: (ESI^+) Calculated for $C_{18}H_{21}N_2O$: 281.1648. Found $[M + H]^+$: 281.1662.

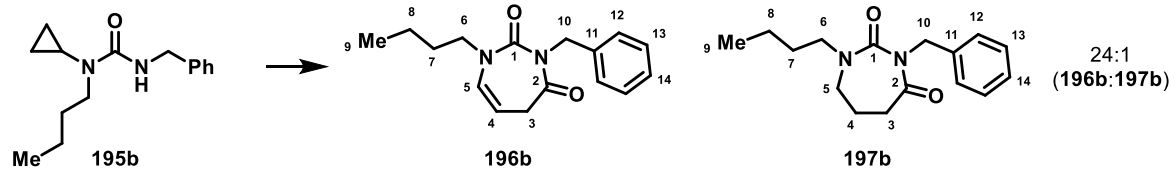
1,3-Dibenzyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (196a) *and* 1,3-Dibenzyl-1,3-diazepane-2,4-dione (197a)



General Procedure B: Urea **195a** (53.2 mg, 0.150 mmol) and $[Rh(cod)_2]$BARF (3.5 mol%) were employed, and the reaction was stirred for 24 h at 100 °C. The crude mixture was purified by FCC (25% EtOAc/hexane) to yield the title compound **196a** (37.5 mg, 82%) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 20:1 (**196a**:**197a**) mixture of products. An analytical sample of **197a** was also isolated for characterisation. **Data for major compound 196a:** ν_{max} / cm^{-1}: 1699 (s), 1647 (s), 1406 (s), 1395 (s), 1212 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.21 (8H, m, 2 × C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 7.05–7.03 (2H, m, 2 × C**8**-H), 6.03 (1H, d, *J* = 7.0 Hz, C**5**-H), 5.54 (1H, dt, *J* = 7.0, 7.0 Hz, C**4**-H), 5.05 (2H, s, C**11**-H_2), 4.73 (2H, s, C**6**-H_2), 3.08 (2H, d, *J* = 7.0 Hz, C**3**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0 (C**2**), 153.9 (C**1**), 137.6 (C**12**), 136.1 (C**7**), 130.3 (C**5**), 128.7. 128.4, 128.1, 127.8, 127.6, 127.3 (C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 112.7 (C**4**), 53.0 (C**6**), 47.9 (C**11**), 35.0 (C**3**); HRMS: (ESI^+) Calculated for $C_{19}H_{18}N_2NaO_2$: 329.1260. Found $[M + Na]^+$: 329.1249. *The structure of this compound was confirmed by 2D NMR analysis. Key HMBC correlations are included on the compound structure above.* **Data for minor compound 197a:** ν_{max} / cm^{-1}: 1694 (s),

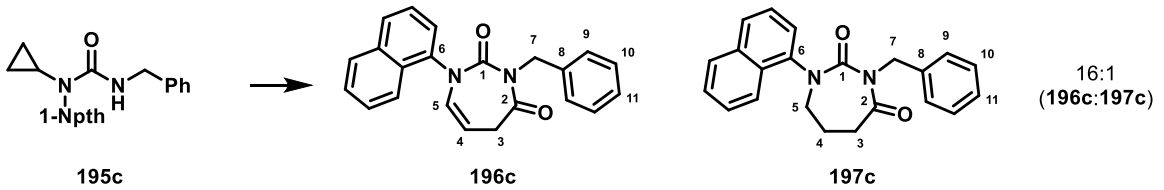
1656 (s), 1421 (s), 1214 (s), 1158 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.23 (8H, m, 2 × C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 7.09–7.06 (2H, m, 2 × C**8**-H), 4.94 (2H, s, C**11**-H_2), 4.60 (2H, s, C**6**-H_2), 3.18 (2H, t, *J* = 7.0 Hz, C**5**-H_2), 2.54 (2H, t, *J* = 7.0 Hz, C**3**-H_2), 1.86 (2H, tt, *J* = 7.0, 7.0 Hz, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3 (C**2**), 157.6 (C**1**), 137.8 (C**12**), 136.7 (C**7**), 128.8, 128.7, 128.5, 127.8, 127.5 (C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 51.8 (C**6**), 46.8 (C**11**), 45.6 (C**5**), 33.7 (C**3**), 25.7 (C**4**); HRMS: (ESI$^+$) Calculated for $C_{19}H_{20}N_2NaO_2$: 331.1417. Found [M + Na]$^+$: 331.1416. *The structure of this compound was confirmed by 2D NMR. Key HMBC correlations are included on the compound structure above.*

1-Benzyl-3-butyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (196b) ***and*** **3-Benzyl-1-butyl-1,3-diazepane-2,4-dione (197b)**



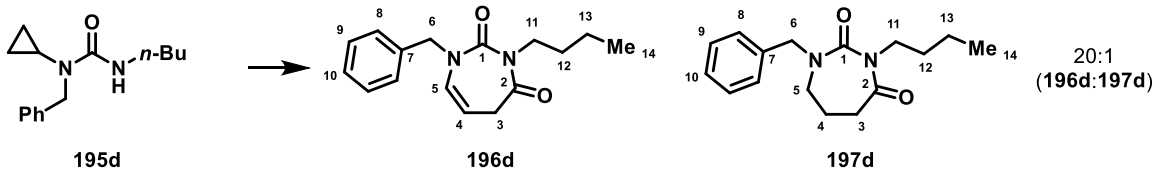
General Procedure B: *Urea **195b** was synthesised by McCreanor*[103]: Urea **195b** (37.0 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (3.5 mol%) were employed, and the reaction was stirred for 25 h at 100 °C. The crude mixture was purified by FCC (30% EtOAc/hexane) to yield the title compound **196b** (33.3 mg, 82%) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 24:1 (**196b**:**197b**) mixture of products. The minor product **197b** was not isolated. **Data for major compound 196b:** ν_{max} / cm^{-1}: 2958 (m), 1699 (s), 1647 (s), 1408 (s), 1212 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.20 (5H, m, 2 × C**12**-H, 2 × C**13**-H, C**14**-H), 6.04 (1H, d, *J* = 7.0 Hz, C**5**-H), 5.56 (1H, dt, *J* = 7.0, 7.0 Hz, C**4**-H), 5.00 (2H, s, C**10**-H_2), 3.55 (2H, t, *J* = 7.0 Hz, C**6**-H_2), 3.09 (2H, d, *J* = 7.0 Hz, C**3**-H_2), 1.56–1.48 (2H, m, C**7**-H_2), 1.31–1.22 (2H, m, C**8**-H_2), 0.90 (3H, t, *J* = 7.0 Hz, C**9**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1 (C**2**), 153.6 (C**1**), 137.7 (C**11**), 130.7 (C**5**), 128.3, 127.8, 127.1 (C**12**, C**13**, C**14**), 112.4 (C**4**), 49.9 (C**6**), 48.0 (C**10**), 34.9 (C**3**), 30.2 (C**7**), 19.9 (C**8**), 13.7 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{16}H_{20}N_2NaO_2$: 295.1417. Found [M + Na]$^+$: 295.1419. **Data for minor compound 197b:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.60 (2H, t, *J* = 7.0 Hz, C**3**-H_2).

1-Benzyl-3-(naphthalen-1-yl)-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (196c) ***and*** **3-Benzyl-1-(naphthalen-1-yl)-1,3-diazepane-2,4-dione (197c)**



General Procedure B: *Urea **195c** was synthesised by McCreanor*[103]: Urea **195c** (47.5 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (5.0 mol%) were employed, and the reaction was stirred for 72 h at 100 °C. The crude mixture was purified by FCC (30% EtOAc/hexane) to yield the title compound **196c** (31.0 mg, 60%) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 16:1 (**196c**:**197c**) mixture of products. The minor product **197c** was not isolated. **Data for major compound 196c:** ν_{max} / cm^{-1}: 2960 (s), 1701 (s), 1652 (s), 1394 (s), 1201 (s), 1141 (m); 1H NMR ($CDCl_3$, 400 MHz): δ 7.88–7.86 (2H, m, 2 × ArC**H**), 7.49–7.45 (2H, m, 2 × ArC**H**), 7.40–7.35 (5H, m, 2 × C**9**-H, 2 × C**10**-**H**, C**11**-**H**), 7.28–7.24 (2H, m, 2 × ArC**H**), 6.93 (1H, d, *J* = 8.5 Hz, 1 × ArC**H**), 6.11 (1H, dd, *J* = 7.0, 1.0 Hz, C**5**-**H**), 5.65 (1H, dt, *J* = 7.0, 7.0 Hz, C**4**-**H**), 5.36 (1H, d, *J* = 14.5 Hz, 1 × C**7**-**H**), 4.90 (1H, d, *J* = 14.5 Hz, 1 × C**7**-**H**), 3.50–3.40 (2H, m, C**3**-**H**$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9 (C**2**), 153.6 (C**1**), 137.4 (C**8**), 137.3 (C**6**), 134.6 (Ar**C**), 131.6 (C**5**), 129.4 128.8, 128.7, 128.5, 128.5, 127.5 (C**9**, C**10**, C**11**, 3 × Ar**C**), 127.3, 126.5, 126.0, 125.5, 121.8 (5 × Ar**C**H), 111.1 (C**4**), 48.0 (C**7**), 35.0 (C**3**); HRMS: (ESI$^+$) Calculated for $C_{22}H_{18}N_2NaO_2$: 365.1260. Found [M + Na]$^+$: 365.1265. **Data for minor compound 197c:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.26 (2H, t, *J* = 7.0 Hz, C**5**-**H**$_2$).

3-Benzyl-1-butyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (196d) ***and*** **1-Benzyl-3-butyl-1,3-diazepane-2,4-dione (197d)**

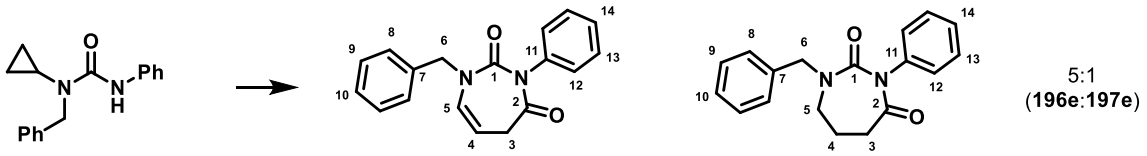


195d **196d** **197d**

General Procedure B: *Urea **195d** was synthesised by McCreanor*[103]: Urea **195d** (37.0 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (5.0 mol%) were employed, and the reaction was stirred for 24 h at 100 °C. The crude mixture was purified by FCC (20% EtOAc/hexane) to yield the title compound **196d** (35.2 mg, 85%) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 20:1 (**196d**:**197d**) mixture of products. The minor product **197d** was not isolated. **Data for major compound 196d:** ν_{max} / cm^{-1}: 2958 (m), 1698 (s), 1645 (s), 1407 (s), 1214 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.26 (5H, m, 2 × C**8**-**H**, 2 × C**9**-**H**, C**10**-**H**), 6.10 (1H, d, *J* = 7.0 Hz, C**5**-**H**), 5.52 (1H, dt, *J* = 7.0, 7.0 Hz, C**4**-**H**), 4.79 (2H, s, C**6**-**H**$_2$), 3.80 (2H, t, *J* = 7.0 Hz, C**11**-**H**$_2$), 2.99 (2H, d, *J* = 7.0 Hz, C**3**-**H**$_2$), 1.55 (2H, tt, *J* = 7.0, 7.0 Hz, C**12**-**H**$_2$), 1.27 (2H, tq, *J* = 7.0, 7.0 Hz, C**13**-**H**$_2$), 0.90 (3H, t, *J* = 7.0 Hz, C**14**-**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1 (C**2**), 154.4 (C**1**), 136.6 (C**7**), 130.5 (C**5**), 128.8, 127.9, 127.8 (C**8**, C**9**, C**10**), 113.0 (C**4**), 53.2 (C**6**), 45.4 (C**11**), 35.2 (C**3**), 30.4 (C**12**), 20.1 (C**13**), 13.8 (C**14**); HRMS: (ESI$^+$) Calculated for $C_{16}H_{20}N_2NaO_2$: 295.1417. Found [M + Na]$^+$: 295.1421. **Data for minor compound 197d:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.66 (2H, s, C**6**-**H**$_2$),

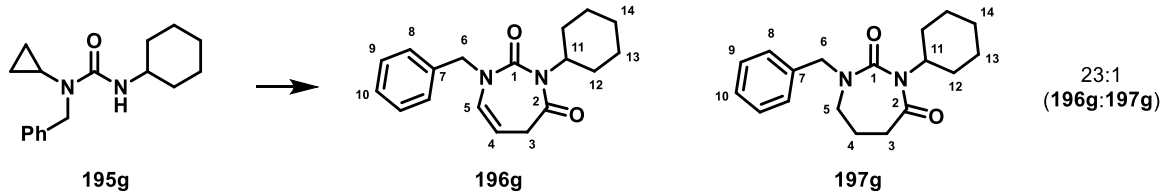
3.75 (2H, t, *J* = 7.0 Hz, C**11**-H$_2$), 3.36 (2H, t, *J* = 7.0 Hz, C**5**-H$_2$), 2.50 (2H, t, *J* = 7.0 Hz, C**3**-H$_2$); HRMS: (ESI$^+$) Calculated for $C_{16}H_{22}N_2NaO_2$: 297.1573. Found [M + Na]$^+$: 297.1575.

3-Benzyl-1-phenyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (196e) ***and*** **1-Benzyl-3-phenyl-1,3-diazepane-2,4-dione (197e)**



General Procedure B: *Urea **195e** was synthesised by McCreanor*[103]: Urea **195e** (40.0 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (7.5 mol%) were employed, and the reaction was stirred for 70 h at 100 °C. The crude mixture was purified by FCC (15–25% EtOAc/hexane) to yield the title compound **196e** (12.2 mg, 28%) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 5:1 (**196e**:**197e**) mixture of products. The minor product **197e** was not isolated. **Data for major compound 196e:** ν_{max} / cm^{-1}: 2987 (s), 1705 (s), 1652 (s), 1403 (s), 1392 (s), 1226 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.19 (10H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H, 2 × C**12**-H, 2 × C**13**-H, C**14**-H), 6.26 (1H, d, *J* = 7.0 Hz, C**5**-H), 5.66 (1H, dt, *J* = 7.0, 7.0 Hz, C**4**-H), 4.81 (2H, s, C**6**-H$_2$), 3.17 (2H, d, *J* = 7.0 Hz, C**3**-H$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5 (C**2**), 153.7 (C**1**), 138.8 (C**11**), 136.4 (C**7**), 130.8 (C**5**), 129.1, 128.8, 128.5, 128.3, 128.1, 128.0 (C**8**, C**9**, C**10**, C**12**, C**13**, C**14**), 113.3 (C**4**), 53.5 (C**6**), 35.2 (C**3**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{16}N_2NaO_2$: 315.1104. Found [M + Na]$^+$: 315.1092. **Data for minor compound 197e:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.26 (2H, t, *J* = 7.0 Hz, C**5**-H$_2$).

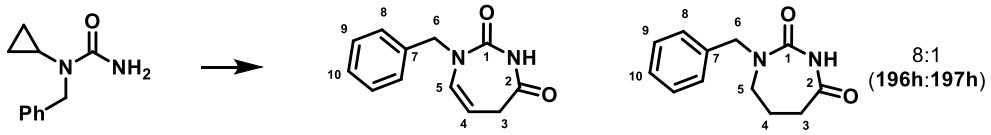
3-Benzyl-1-cyclohexyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (196g) ***and*** **1-Benzyl-3-cyclohexyl-1,3-diazepane-2,4-dione (197g)**



General Procedure B: *Urea **195g** was synthesised by McCreanor*[103]: Urea **195g** (40.9 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (7.5 mol%) were employed, and the reaction was stirred for 24 h at 100 °C. The crude mixture was purified by FCC (20% EtOAc/hexane) to yield the title compound **196g** (31.0 mg, 69%) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 23:1 (**8d**:**9d**) mixture of products. The minor product **197g** was not isolated. **Data for major compound 196d:** ν_{max} / cm^{-1}: 2928 (s), 1695 (s), 1648 (s), 1406 (s), 1394 (s), 1223 (s), 1049 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.24 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 6.09 (1H, d, *J* = 7.0 Hz, C**5**-H), 5.55 (1H, dt, *J* = 7.0,

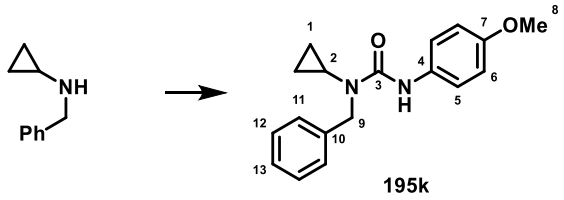
7.0 Hz, C**4**-H), 4.77 (2H, s, C**6**-H$_2$), 4.14 (1H, tt, *J* = 12.0, 3.5 Hz, C**11**-H), 2.93 (2H, d, *J* = 7.0 Hz, C**3**-H$_2$), 2.08–1.98 (2H, m, 2 × C**12**-H), 1.81–1.63 (5H, m, 2 × C**12**-H, 2 × C**13**-H, 1 × C**14**-H), 1.38–1.11 (3H, m, 2 × C**13**-H, 1 × C**14**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.5 (C**2**), 153.9 (C**1**), 136.5 (C**7**), 130.3 (C**5**), 128.8, 127.9, 127.8 (C**8**, C**9**, C**10**), 114.3 (C**4**), 57.5 (C**11**), 52.7 (C**6**), 35.4 (C**3**), 29.9 (C**12**), 26.3 (C**13**), 25.4 (C**14**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{22}N_2NaO_2$: 321.1573. Found [M + Na]$^+$: 321.1568. **Data for minor compound 197g:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.64 (2H, s, C**6**-H$_2$).

3-Benzyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (196h) *and* 1-Benzyl-1,3- diazepane-2,4-dione (196h)



General Procedure B: *Urea **195h** was synthesised by McCreanor*[103]: Urea **195h** (28.5 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (5.0 mol%) were employed, and the reaction was stirred for 72 h at 100 °C. The crude mixture was purified by FCC (45% EtOAc/hexane) to yield the title compound **196h** (17.5 mg, 54%) as a beige oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed an 8:1 (**196h**:**197h**) mixture of products. The minor product **197h** was not isolated. **Data for major compound 196h:** ν_{max} / cm^{-1}: 3215 (m), 2987 (s), 1653 (s), 1412 (s), 1388 (s), 1260 (s), 1075 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (1H, br. s, NH), 7.38–7.24 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 6.09 (1H, d, *J* = 7.5 Hz, C**5**-H), 5.42 (1H, dt, *J* = 7.5, 7.0 Hz, C**4**-H), 4.78 (2H, s, C**6**-H$_2$), 3.06 (2H, d, *J* = 7.0 Hz, C**3**-H$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1 (C**2**), 151.2 (C**1**), 136.2 (C**7**), 130.8 (C**5**), 128.9, 128.0, 127.9 (C**8**, C**9**, C**10**), 110.4 (C**4**), 52.6 (C**6**), 34.3 (C**3**); HRMS: (ESI$^+$) Calculated for $C_{12}H_{12}N_2NaO_2$: 239.0790. Found [M + Na]$^+$: 239.0787. **Data for minor compound 197h:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.41 (2H, t, *J* = 7.0 Hz, C**5**-H$_2$).

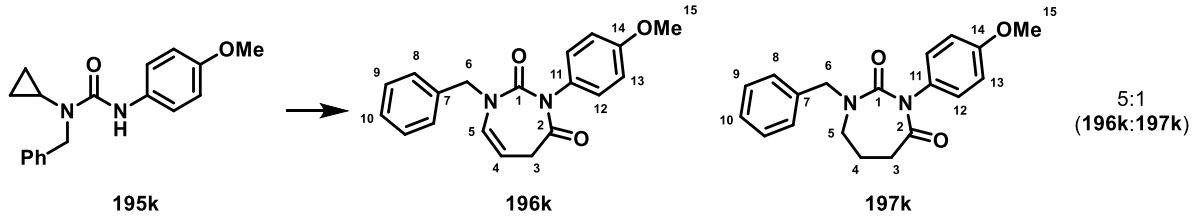
1-Benzyl-1-cyclopropyl-3-(4-methoxyphenyl)urea (195k)



General procedure A: Benzylcyclopropylamine (700 mg, 4.80 mmol) and 4-methoxyphenyl isocyanate (0.560 mL, 4.30 mmol) were employed to yield a crude mixture, which was purified by FCC (25% EtOAc/hexane) to yield the title compound (1.17 g, 91%) as a colourless solid; m.p. 88–90 °C (CH_2Cl_2/hexane) ν_{max} / cm^{-1}: 3352 (m), 1639 (s), 1510 (s), 1412 (m), 1225 (s), 1170 (m), 1035 (s); ^{1}H

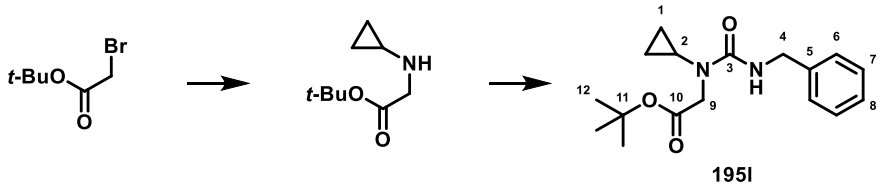
NMR (500 MHz, $CDCl_3$): δ 7.28–7.32 (5H, m, 2 × C**11**-H, 2 × C**12**-H, C**13**-H), 7.37 (2H, m, 2 × C**6**-H), 7.21 (1H, br. s, NH), 6.86 (2H, m, 2 × C**5**-H), 4.62 (2H, s, C**9**-H_2), 3.79 (3H, s, C**8**-H_3), 2.50 (1H, m, C**2**-H), 0.94–0.86 (4H, m, 4 × C**1**-H_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6 (C**3**), 155.8 (C**7**), 138.8 (C**10**), 132.2 (C**4**), 128.6, 128.1 (C**11**, C**12**), 127.2 (C**13**), 121.8 (C**6**), 114.3 (C**5**), 55.6 (C**8**), 50.5 (C**9**), 28.2 (C**2**), 9.1 (C**1**); *m/z* (ESI^+) HRMS: Calculated for $C_{18}H_{20}N_2NaO_2$: 319.1417. Found $[M + Na]^+$: 319.1422.

3-Benzyl-1-phenyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (196k) *and* 1-Benzyl-3-(4-methoxyphenyl)-1,3-diazepane-2,4-dione (197k)



General Procedure B: Urea **195k** (44.5 mg, 0.150 mmol) and $Rh(cod)_2BARF$ (7.5 mol%) were employed and the reaction was stirred for 90 h at 100 °C. The crude mixture was purified by FCC (40% EtOAc/hexane) to yield the title compound **196k** (13.5 mg, 28%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 5:1 (**196k**:**197k**) mixture of products. The minor product **197k** was not isolated. **Data for major compound 196k:** ν_{max} / cm^{-1}: 2934 (m), 1705 (m), 1652 (s), 1509 (s), 1391 (s), 1230 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.29 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 7.12 (2H, m, 2 × C**13**-H), 6.94 (2H, m, 2 × C**12**-H), 6.25 (1H, d, *J* = 7.0 Hz, C**5**-H), 5.65 (1H, dd, *J* = 7.0, 7.0 Hz, C**4**-H), 4.80 (2H, s, C**6**-H_2), 3.81 (3H, s, C**15**-H_3), 3.16 (2H, d, *J* = 7.0 Hz, C**3**-H_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9 (C**2**), 159.3 (C**14**), 154.1 (C**1**), 136.6 (C**7**), 131.6 (C**11**), 131.0 (C**10**), 129.6 (C**13**), 129.0, 128.2 (C**8**, C**9**), 114.6 (C**12**), 113.5 (C**4**), 55.5 (C**15**), 53.6 (C**6**), 35.3 (C**3**); *m/z* (ESI^+) HRMS: Calculated for $C_{19}H_{18}N_2NaO_3$: 345.1210. Found $[M + Na]^+$: 345.1215.

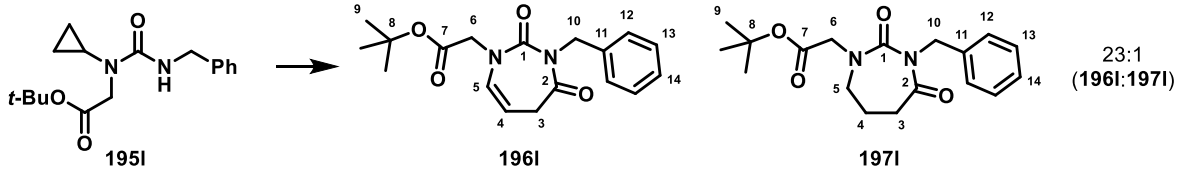
***tert*-Butyl *N*-(benzylcarbamoyl)-*N*-cyclopropylglycinate (195l)**



To a solution of cyclopropylamine (1.04 mL, 15.0 mmol) and NEt_3 (2.79 mL, 20.0 mmol) in CH_2Cl_2 (20 mL) was added *t*-butyl bromoacetate (1.48 mL, 10.0 mmol) at room temperature. The reaction mixture was stirred for 7 h before cooling to 0 °C. Benzyl isocyanate (1.84 mL, 20.0 mmol) was added and the reaction mixture was warmed to room temperature with stirring for a further 17 h. The resulting solution was diluted with CH_2Cl_2 (25 mL) and washed with water (30 mL), 1 M aq. HCl (30 mL), sat.

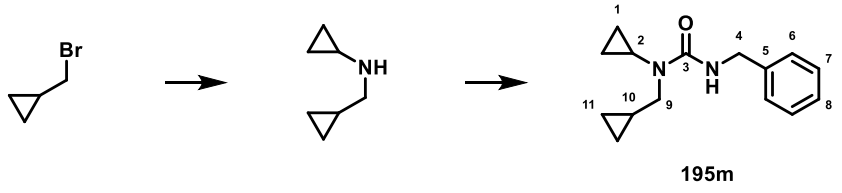
aq. $NaHCO_3$ (30 mL) and brine (30 mL) before being dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by FCC (40–50% EtOAc/hexane) to yield the title compound **195l** (1.50 g, 49%) as a colourless solid; m.p. 70–72 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3359 (s), 2973 (w), 1749 (s), 1639 (s), 1526 (s), 1220 (s), 1151 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.31 (4H, m, 2 × C**6**-H, 2 × C**7**-H), 7.26 (1H, m, C**8**-H), 5.67 (1H, br. s, NH), 4.49 (2H, d, *J* = 5.5 Hz, C**4**-H_2), 3.99 (2H, s, C**9**-H_2), 2.71 (1H, m, C**2**-H), 1.47 (9H, s, C**12**-H_3), 0.80 (2H, m, 2 × C**1**-H), 0.73 (2H, m, 2 × C**1**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1 (C**10**), 158.9 (C**3**), 139.7 (C**5**), 128.7 (C**6**), 127.6 (C**7**), 127.3 (C**8**), 81.5 (C**11**), 50.1 (C**9**), 44.8 (C**4**), 28.7 (C**2**), 28.3 (C**12**), 8.8 (C**1**); HRMS: (ESI^+) Calculated for $C_{17}H_{24}N_2NaO_3$: 327.1679. Found $[M + H]^+$: 327.1684.

***tert*-Butyl 2-(3-benzyl-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-1-yl)acetate (196l) *and tert*-Butyl 2-(3-benzyl-2,4-dioxo-1,3-diazepan-1-yl)acetate (197l)**



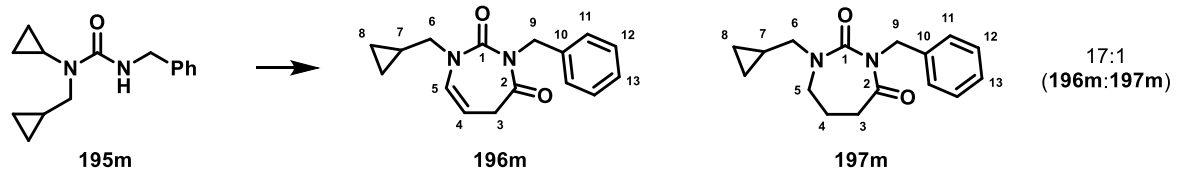
General Procedure B: Urea **195l** (45.7 mg, 0.150 mmol) and $[Rh(cod)_2]BARF$ (5.0 mol%) were employed, and the reaction was stirred for 48 h at 100 °C. The crude mixture was purified by FCC (20% EtOAc/hexane) to yield the title compound **196l** (32.4 mg, 65%) as a colourless oil. Analysis of the crude reaction mixture by ^1H NMR revealed a 23:1 (**196l**:**197l**) mixture of products. The minor product **197l** was not isolated. **Data for major compound 196l:** m.p. 113–116 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 2976 (w), 1747 (s), 1696 (s), 1647 (s), 1438 (s), 1219 (s), 1152 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.19 (5H, m, 2 × C**12**-H, 2 × C**13**-H, C**14**-H), 6.02 (1H, d, *J* = 7.0 Hz, C**5**-H), 5.61 (1H, dt, *J* = 7.0, 7.0 Hz, C**4**-H), 5.00 (2H, s, C**10**-H_2), 4.14 (2H, s, C**6**-H_2), 3.29 (2H, d, *J* = 7.0 Hz, C**3**-H_2), 1.44 (9H, s, C**9**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5 (C**2**), 167.3 (C**7**), 154.3 (C**1**), 137.7 (C**11**), 130.9 (C**5**), 128.5, 127.9, 127.3 (C**12**, C**13**, C**14**), 113.7 (C**4**), 82.7 (C**8**), 52.0 (C**6**), 48.2 (C**10**), 35.1 (C**3**), 28.2 (C**9**); HRMS: (ESI^+) Calculated for $C_{18}H_{22}N_2NaO_4$: 353.1472. Found $[M + Na]^+$: 353.1476. **Data for minor compound 197l:** *Characteristic signals only*: ^1H NMR ($CDCl_3$, 400 MHz): δ 2.83 (2H, t, *J* = 7.0 Hz, C**5**-H_2).

3-Benzyl-1-cyclopropyl-1-(cyclopropylmethyl)urea (195m)



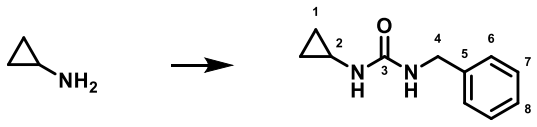
(Bromomethyl)cyclopropane (0.970 mL, 10.0 mmol) was added to a stirring solution of cyclopropylamine (2.08 mL, 30.0 mmol) in DMSO (25 mL) at room temperature. The reaction was stirred for 20 h before being diluted with CH_2Cl_2 (200 mL) and washed with water (2 × 200 mL) and brine (200 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* (care was taken as the secondary amine was presumed to be volatile). The crude amine was dissolved in CH_2Cl_2 (33 mL) and cooled to 0 °C before adding benzyl isocyanate (1.12 mL, 9.09 mmol). The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated *in vacuo* to yield a crude mixture which was purified by FCC (25% EtOAc/hexane) to yield the title compound **195m** (1.10 g, 45%) as a colourless solid; m.p. 74–75 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3375 (s), 2922 (w), 1640 (s), 1628 (s), 1509 (s), 1274 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.18 (5H, m, 2 × C**6**-H, 2 × C**7**-H, C**8**-H), 5.54 (1H, br. s, NH), 4.42 (2H, d, *J* = 6.0 Hz, C**4**-H_2), 3.18 (2H, d, *J* = 7.0 Hz, C**9**-H_2), 2.54 (1H, m, C**2**-H), 1.00 (1H, m, C**10**-H), 0.76 (2H, m, C**1**-H_2), 0.65 (2H, m, C**1**-H_2), 0.41 (2H, m, C**11**-H_2), 0.20 (2H, m, C**11**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1 (C**3**), 140.0 (C**5**), 128.7 (C**7**), 127.6 (C**6**), 127.2 (C**8**), 51.4 (C**9**), 44.8 (C**4**), 27.7 (C**2**), 10.1 (C**10**), 9.1 (C**1**), 3.5 (C**11**); HRMS: (ESI^+) Calculated for $C_{15}H_{20}N_2NaO$: 267.1468. Found $[M + Na]^+$: 267.1470.

1-Benzyl-3-(cyclopropylmethyl)-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (196m) *and* 3-Benzyl-1-(cyclopropylmethyl)-1,3-diazepane-2,4-dione (197m)



General Procedure B: Urea **195m** (36.7 mg, 0.150 mmol) and $[Rh(cod)_2]$BARF (3.5 mol%) were employed, and the reaction was stirred for 24 h at 100 °C. The crude mixture was purified by FCC (20% EtOAc/hexane) to yield the title compound **196m** (35.0 mg**,** 86%) as a brown oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 20:1 (**196m**:**197m**) mixture of products. The minor product **197m** was not isolated. **Data for major compound 196m:** ν_{max} / cm^{-1}: 3003 (w), 1699 (s), 1648 (s), 1409 (s), 1214 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.19 (5H, m, 2 × C**11**-H, 2 × C**12**-H, C**13**-H), 6.13 (1H, d, *J* = 7.0 Hz, C**5**-H), 5.59 (1H, dt, *J* = 7.0, 7.0 Hz, C**4**-H), 5.01 (2H, s, C**9**-H_2), 3.46 (2H, d, *J* = 7.0 Hz, C**6**-H_2), 3.14 (2H, d, *J* = 7.0 Hz, C**3**-H_2), 1.04 (1H, m, C**7**-H), 0.49 (2H, m, 2 × C**8**-H), 0.26 (2H, m, C**8**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4 (C**2**), 153.9 (C**1**), 137.9 (C**10**), 130.9 (C**5**), 128.4, 127.9, 127.2 (C**11**, C**12**, C**13**), 112.7 (C**4**), 54.5 (C**6**), 48.1 (C**9**), 35.1 (C**3**), 10.2 (C**7**), 3.6 (C**8**); HRMS: (ESI^+) Calculated for $C_{16}H_{18}N_2NaO_2$: 293.1260. Found $[M + Na]^+$: 293.1270. **Data for minor compound 9i:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.65 (2H, t, *J* = 7.5 Hz, C**3**-H_2).

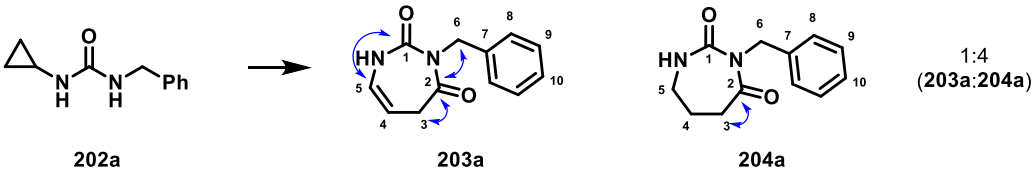
1-Benzyl-3-cyclopropylurea (202a)



202a

General procedure A: Cyclopropylamine (0.762 mL, 11.0 mmol) and benzyl isocyanate (1.09 mL, 10.0 mmol) were employed. The crude mixture was purified by recrystallisation (CH_2Cl_2/hexane) to yield the title compound **202a** (1.58 g, 83%) as a colourless solid; m.p. 139–140 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3309 (s), 1623 (s), 1574 (s), 1453 (m), 1255 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.25 (2 × C**6**-H, 2 × C**7**-H, C**8**-H), 5.31 (1H, br. s, NH), 4.79 (1H, br. s, NH), 4.47 (2H, d, *J* = 6.0 Hz, C**4**-H_2), 2.46 (1H, tt, *J* = 7.0, 3.5 Hz, C**2**-H), 0.76–0.71 (2H, m, 2 × C**1**-H), 0.60–0.57 (2H, m, 2 × C**1**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.9 (C**3**), 139.4 (C**5**), 128.6, 127.4, 127.3 (C**6**, C**7**, C**8**), 44.2 (C**4**), 22.4 (C**2**), 7.6 (C**1**); HRMS: (ESI^+) Calculated for $C_{11}H_{14}N_2NaO$: 213.0998. Found $[M + Na]^+$: 213.0997. *The spectroscopic properties of this compound were consistent with the data available in the literature.*[355]

3-Benzyl-1,3-diazepane-2,4-dione (204a) ***and*** **1-Benzyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (203a)**

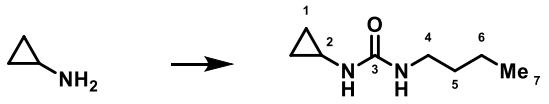


202a **203a** **204a**

General Procedure B: Urea **202a** (28.5 mg, 0.150 mmol) and $[Rh(cod)_2]BARF$ (5.0 mol%) were employed, and the reaction was stirred for 23 h at 90 °C. The crude mixture was purified by FCC (30% EtOAc/hexane) to yield the title compound **204a** (20.3 mg**,** 62%, 1:4, **203a**:**204a**) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 1:4 (**203a**:**204a**) mixture of products. **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 3300 (m), 2987 (s), 1705 (s), 1537 (s), 1381 (s), 1255 (s). **Data for major compound 204a:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.79 (1H, br. s, NH), 7.35–7.21 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 4.50 (2H, d, *J* = 6.0 Hz, C**6**-H_2), 3.89 (2H, t, *J* = 7.0 Hz, C**5**-H_2), 2.61 (2H, t, *J* = 7.0 Hz, C**3**-H_2), 2.04 (2H, tt, *J* = 7.0, 7.0 Hz, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.1 (C**2**), 153.0 (C**1**), 138.3 (C**7**), 128.6, 127.4, 127.3 (C**8**, C**9**, C**10**), 45.7 (C**5**), 43.8 (C**6**), 33.4 (C**3**), 17.1 (C**4**); HRMS: (ESI^+) Calculated for $C_{12}H_{14}N_2NaO_2$: 241.0947. Found $[M + Na]^+$: 241.0963. *The structure of this compound was confirmed by 2D NMR. Key HMBC correlations are included on the compound structure above.* **Data for minor compound 203a:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.79 (1H, br. s, NH), 7.35–7.21 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 6.12 (1H, dd, *J* = 7.0, 4.0 Hz, C**5**-H), 5.44 (1H, dt, *J* = 7.0, 7.0 Hz, C**4**-H), 5.01 (2H, s, C**6**-H_2), 3.20 (2H, d, *J* = 7.0 Hz, C**3**-H_2); ^{13}C NMR ($CDCl_3$,

100 MHz): δ 169.0 (C**2**), 154.2 (C**1**), 137.5 (C**7**), 128.3, 127.9, 127.3 (C**8**, C**9**, C**10**), 126.0 (C**5**), 110.1 (C**4**), 48.0 (C**6**), 35.2 (C**3**); HRMS: (ESI$^+$) Calculated for $C_{12}H_{12}N_2O_2$: 216.0899. Found [M]$^+$: 216.0898. *The structure of this compound was confirmed by 2D NMR. Key HMBC correlations are included on the compound structure above.*

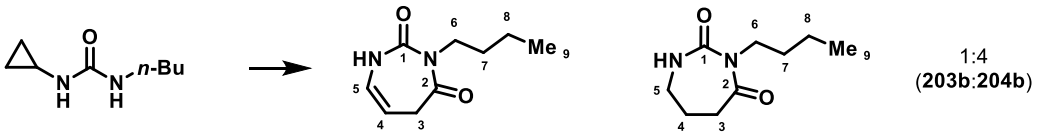
1-Butyl-3-cyclopropylurea (202b)



202b

General procedure A: Cyclopropylamine (0.760 mL, 11.0 mmol) and *n*-butyl isocyanate (1.13 mL, 10.0 mmol) were employed. The crude mixture was purified by FCC (75% EtOAc/hexane) to yield the title compound **202b** (1.29 g, 83%) as a colourless solid; m.p. 73–74 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3305 (m), 2931 (m), 1626 (s), 1564 (s), 1250 (m), 1224 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.00 (1H, br. s, N<u>H</u>), 4.86 (1H, br. s, N<u>H</u>), 3.22 (2H, m, C**4**-<u>H</u>$_2$), 2.41 (1H, m, C**2**-<u>H</u>), 1.49 (2H, m, C**5**-<u>H</u>$_2$), 1.35 (2H, m, C**6**-<u>H</u>$_2$), 0.92 (3H, t, *J* = 7.0 Hz, C**7**-<u>H</u>$_3$), 0.73–0.52 (4H, m, C**1**-<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3 (C**3**), 40.1 (C**4**), 32.5 (C**5**), 22.5 (C**2**), 20.2 (C**6**), 13.9 (C**7**), 7.6 (C**1**); HRMS: (ESI$^+$) Calculated for $C_8H_{16}N_2NaO$: 179.1155. Found [M + H]$^+$: 179.1160.

3-Butyl-1,3-diazepane-2,4-dione (204b) ***and*** **1-Butyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (203b)**



202b **203b** **204b** 1:4 (**203b**:**204b**)

General Procedure B: Urea **202b** (23.4 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (5.0 mol%) were employed, and the reaction was stirred for 47 h at 90 °C. The crude mixture was purified by FCC (40% EtOAc/hexane) to yield the title compound **204b** (19.8 mg**,** 72%, 5:1, **204b**:**203b**) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 4:1 (**204b**:**203b**) mixture of products. **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 3307 (w), 2958 (w), 1708 (s), 1541 (s), 1381 (s), 1255 (s). **Data for the major product 204b:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (1H, br. s, N<u>H</u>), 3.85 (2H, t, *J* = 7.0 Hz, C**5**-<u>H</u>$_2$), 3.29 (2H, m, C**6**-<u>H</u>$_2$), 2.59 (2H, t, *J* = 8.0 Hz, C**3**-<u>H</u>$_2$), 2.02 (2H, m, C**4**-<u>H</u>$_2$), 1.52 (2H, m, C**7**-<u>H</u>$_2$), 1.36 (2H, m, C**8**-<u>H</u>$_2$), 0.92 (3H, t, *J* = 7.0 Hz, C**9**-<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.1 (C**2**), 153.1 (C**1**), 45.8 (C**5**), 39.7 (C**6**), 33.6 (C**3**), 30.5 (C**7**), 20.2 (C**8**), 17.2 (C**4**), 13.9 (C**9**); HRMS: (ESI$^+$) Calculated for $C_9H_{16}N_2NaO_2$: 207.1104. Found [M + Na]$^+$: 207.1100. **Data for the minor product 203b:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (1H,

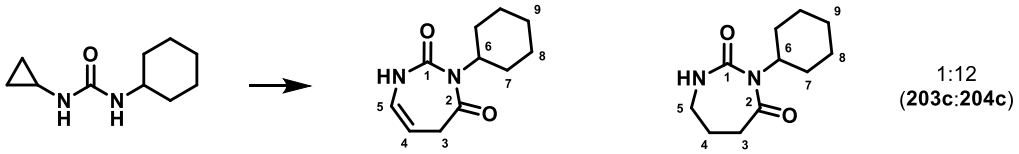
br. s, NH), 6.15 (1H, dd, *J* = 7.0, 7.0 Hz, C**5**-H), 5.42 (1H, m, C**4**-H), 3.77 (2H, t, *J* = 7.5 Hz, C**6**-H_2), 3.14 (2H, d, *J* = 7.0 Hz, C**3**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.3 (C**2**), 154.9 (C**1**), 126.1 (C**5**), 110.4 (C**4**), 45.3 (C**6**), 35.5 (C**3**), 31.8 (C**7**), 20.2 (C**8**), 13.9 (C**9**).

1-Cyclohexyl-3-cyclopropylurea (202c)

202c

General Procedure A: Cyclopropylamine (0.760 mL, 11.0 mmol) and cyclohexyl isocyanate (1.28 mL, 10.0 mmol) were employed to yield the title compound **202c** (1.67 g, 92%) as a colourless solid; m.p. 125–126 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3325 (s), 2926 (w), 1629 (s), 1568 (s), 1253 (w); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.84 (1H, br. s, NH), 4.60 (1H, br. s, NH), 3.64 (1H, m, C**4**-H), 2.41 (1H, m, C**2**-H), 1.95 (2H, m, C**5**-H_2), 1.74–1.66 (2H, m, C**6**-H_2), 1.64–1.57 (2H, m, C**7**-H_2), 1.43–1.33 (2H, m, C**6**-H_2), 1.23–1.10 (2H, m, C**5**-H_2), 0.73 (2H, m, 2 × C**1**-H), 0.56 (2H, m, 2 × C**1**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.5 (C**3**), 48.8 (C**4**), 34.0 (C**5**), 25.8 (C**7**), 25.1 (C**6**), 22.5 (C**2**), 7.7 (C**1**); HRMS: (ESI^+) Calculated for $C_{10}H_{18}N_2NaO$: 205.1317. Found $[M + Na]^+$: 205.1311.

3-Cyclohexyl-1,3-diazepane-2,4-dione (204c) ***and*** **1-Cyclohexyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (203c)**



202c **203c** **204c**

General Procedure B: Urea **202c** (27.3 mg, 0.150 mmol) and $[Rh(cod)_2]$BARF (5.0 mol%) were employed, and the reaction was stirred for 51 h at 90 °C. The crude mixture was purified by FCC (25% EtOAc/hexane) to yield the title compound **204c** (21.2 mg, 67%) as a pale yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 12:1 (**204c**:**203c**) mixture of products. The minor product **203c** was not isolated. **Data for the major product 204c:** ν_{max} / cm^{-1}: 3291 (br.), 2929 (br.), 2854 (br.), 17.6 (s), 1534 (s), 1380 (m), 1243 (m), 1219 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (1H, br. m, NH), 3.84 (2H, t, *J* = 7.0 Hz, C**5**-H_2), 3.71 (1H, m, C**6**-H), 2.58 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.00 (2H, tt, *J* = 8.0, 7.0 Hz, C**4**-H_2), 1.92–1.88 (2H, m, 2 × C**7**-H), 1.72–1.67 (2H, m, 2 × C**8**-H), 1.60–1.55 (1H, m, 1 × C**9**-H), 1.41–1.31 (2H, m, 2 × C**8**-H), 1.29–1.15 (3H, m, 2 × C**7**-H, 1 × C**9**-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.1 (C**2**), 152.2 (C**1**), 48.7 (C**6**), 45.8 (C**5**), 33.7 (C**3**), 33.1 (C**7**), 25.7 (C**9**), 24.8 (C**8**), 17.1 (C**4**); HRMS: (ESI^+) Calculated for $C_{11}H_{18}N_2NaO_2$: 233.1260. Found $[M + Na]^+$: 233.1256. **Data**

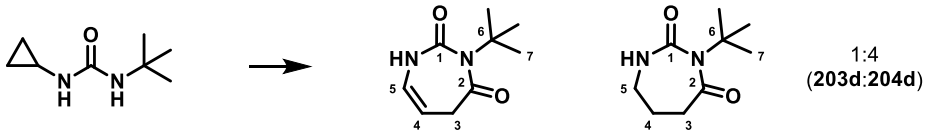
for the minor product 203c: *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.16 (1H, dt, *J* = 6.0, 2.0 Hz, C**4**-H).

1-(*tert*-Butyl)-3-cyclopropylurea (202d)

202d

General Procedure A: Cyclopropylamine (0.380 mL, 5.50 mmol) and *tert*-butyl isocyanate (0.430 mL, 5.00 mmol) were employed to yield the title compound **202d** (461 mg, 59%) as a colourless solid; ν_{max} / cm^{-1}: 3323 (br.), 2965 (m), 1635 (s), 1557 (s), 1453 (m), 1360 (m), 1276 (m), 1218 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.86 (1H, br. s, NH), 4.54 (1H, br. s, NH), 2.38 (1H, m, C**2**-H), 1.35 (9H, s, C**5**-H_3), 0.70 (2H, m, 2 × C**1**-H), 0.53 (2H, m, 2 × C**1**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4 (C**3**), 50.5 (C**4**), 29.6 (C**5**), 22.7 (C**2**), 7.6 (C**1**); HRMS: (ESI+) Calculated for $C_8H_{16}N_2NaO$: 179.1155. Found $[M + Na]^+$: 179.1155.

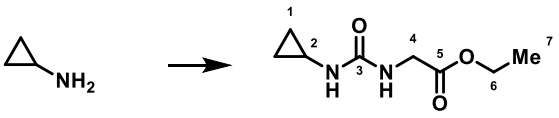
3-(*tert*-Butyl)-1,3-diazepane-2,4-dione (204d) ***and*** **1-(*tert*-Butyl)-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (203d)**



202d **203d** **204d**

General Procedure B: Urea **202d** (23.4 mg, 0.150 mmol) and $[Rh(cod)_2]$BARF (5.0 mol%) were employed, and the reaction was stirred for 48 h at 90 °C. The crude mixture was purified by FCC (50% EtOAc/hexane) to yield the title compound **204d** (21.2 mg, 53%, 5:1, **204d**:**203d**) as a pale yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 4:1 (**204d**:**203d**) mixture of products. **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 3288 (br.), 2966 (br.), 1710 (s), 1547 (s), 1383 (m), 1364 (m), 1263 9m), 1201 (m). **Data for the major product 204d:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41 (1H, br. s, NH), 3.82 (2H, t, *J* = 7.0 Hz, C**5**-H_2), 2.58 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 1.99 (2H, tt, *J* = 8.0, 7.0 Hz, C**4**-H_2), 1.37 (9H, s, C**7**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.0 (C**2**), 151.6 (C**1**), 50.9 (C**6**), 45.6 (C**6**), 33.8 (C**3**), 29.0 (C**7**), 17.0 (C**4**); HRMS: (ESI^+) Calculated for $C_9H_{16}N_2NaO_2$: 207.1104. Found $[M + Na]^+$: 207.1114. **Data for the minor product 203d:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ; 8.34 (1H, br. s, NH), 6.18 (1H, dt, *J* = 6.0, 2.0 Hz, C**5**-H), 4.42 (1H, t, *J* = 2.0 Hz, C**4**-H), 1.40 (9H, s, C**7**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.1 (C**5**), 51.0 (C**3**), 29.1 (C**7**).

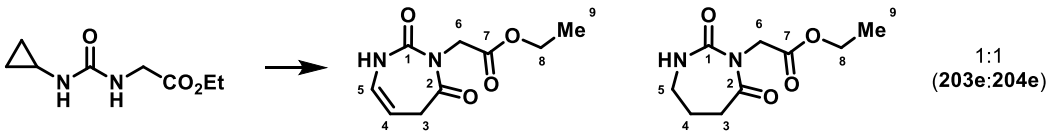
Ethyl (cyclopropylcarbamoyl)glycinate (202e)



202e

General procedure A: Cyclopropylamine (0.760 mL, 11.0 mmol) and ethyl isocyanatoacetate (1.12 mL, 10.0 mmol) were employed to yield the title compound **202e** (777 g, 42%) as a white solid; m.p. 122–123 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3341 (m), 2983 (m), 1741 (s), 1627 (s), 1586 (s), 1410 (m), 1183 (s), 1031 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 5.56 (1H, br. s, N<u>H</u>), 4.98 (1H, br. s, N<u>H</u>), 4.21 (2H, q, *J* = 7.0 Hz, C**6**-<u>H</u>$_2$), 4.03 (2H, d, *J* = 5.5 Hz, C**4**-<u>H</u>$_2$), 2.50 (1H, m, C**2**-<u>H</u>), 1.28 (3H, t, *J* = 7.0 Hz, C**7**-<u>H</u>$_3$), 0.77 (2H, m, 2 × C**1**-<u>H</u>$_2$), 0.62 (2H, m, 2 × C**1**-<u>H</u>$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1 (C**5**), 159.0 (C**3**), 61.5 (C**6**), 42.3 (C**4**), 22.5 (C**2**), 14.3 (C**7**), 7.6 (C**1**); *m/z* (ESI^+) HRMS: Calculated for $C_8H_{14}N_2NaO_3$: 209.0897. Found $[M + Na]^+$: 209.0893.

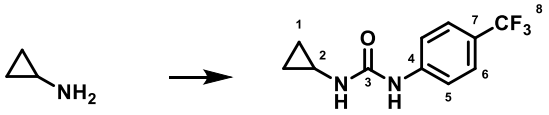
Ethyl 2-(2,7-dioxo-1,3-diazepan-1-yl)acetate and (204e) ***and*** **Ethyl 2-(2,7-dioxo-2,3,6,7-tetrahydro-1*H*-1,3-diazepin-1-yl)acetate (203e)**



202e **203e** **204e** 1:1 (**203e**:**204e**)

General Procedure B: Urea **202e** (27.9 mg, 0.150 mmol) and $Rh(cod)_2BARF$ (5.0 mol%) were employed, and the reaction was stirred for 49 h at 90 °C. The crude mixture was purified by FCC (50% EtOAc/hexane) to yield the title compound **204e** (22.2 mg**,** 69%, 1:1 ratio **204e**:**203e**) as a pale yellow solid. *Compounds could not be separated by FCC.* **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 3310 (m), 2982 (m), 1710 (s), 1656 (s), 1532 (m), 1379 (s), 1204 (s); **Data for saturated compound 204e:** ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (1H, br. s, N<u>H</u>), 6.20 (1H, dd, *J* = 7.0, 4.0 Hz, C**5**-<u>H</u>), 5.43 (1H, dt, *J* = 7.0, 7.0 Hz, C**4**-<u>H</u>), 4.19 (2H, q, *J* = 7.0 Hz, C**8**-<u>H</u>$_2$), 3.24 (2H, d, *J* = 7.0 Hz, C**3**-<u>H</u>$_2$), 1.26 (3H, t, *J* = 7.0 Hz, C**9**-<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7 (C**2**), 168.7 (C**7**), 154.3 (C**1**), 126.3 (C**5**), 109.8 (C**4**), 61.5 (C**8**), 46.3 (C**6**), 34.9 (C**3**), 14.2 (C**9**); *m/z* (ESI^+) HRMS: Calculated for $C_9H_{14}N_2NaO_4$: 237.0846. Found $[M + Na]^+$: 237.0844. **Data for unsaturated compound 203d:** ^1H NMR (400 MHz, $CDCl_3$): δ 8.80 (1H, br. s, N<u>H</u>), 4.21 (2H, q, *J* = 7.0 Hz, C**8**-<u>H</u>$_2$), 4.06 (2H, d, *J* = 5.5 Hz, C**6**-<u>H</u>$_2$), 3.86 (2H, t, *J* = 7.0 Hz, C**5**-<u>H</u>$_2$), 2.61 (2H, t, *J* = 8.0 Hz, C**3**-<u>H</u>$_2$), 2.04 (2H, tt, *J* = 8.0, 7.0 Hz, C**4**-<u>H</u>$_2$), 1.28 (3H, t, *J* = 7.0 Hz, C**9**-<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2 (C**2**), 169.7 (C**7**), 153.2 (C**1**), 61.5 (C**8**), 45.7 (C**5**), 41.8 (C**6**), 33.4 (C**3**), 17.2 (C**4**), 14.2 (C**9**); *m/z* (ESI^+) HRMS: Calculated for $C_9H_{13}N_2O_4$: 213.0870. Found $[M + H]^+$: 213.0873.

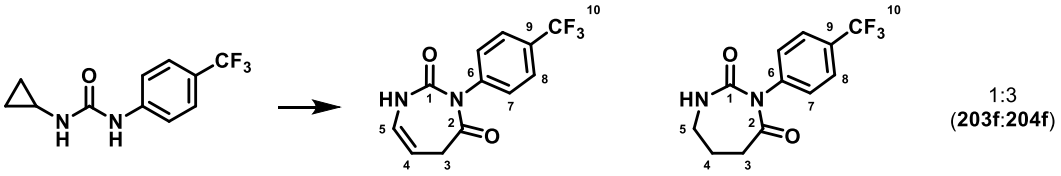
1-Cyclopropyl-3-(4-(trifluoromethyl)phenyl)urea (202f)



202f

General procedure A: Cyclopropylamine (0.380 mL, 5.50 mmol) and 4-(trifluoromethyl)phenyl isocyanate (0.710 mL, 5.00 mmol) were employed to yield the title compound **202f** (1.00 g, 82%) as a colourless solid; m.p. 180–181 °C ($CHCl_3$); ν_{max} / cm^{-1}: 3313 (br.), 1651 (s), 1603 (m), 1544 (s), 1326 (s), 1161 (s), 1107 (s), 1062 (s); ^{1}H NMR (MeOD-d_4, 400 MHz): δ 7.58–7.51 (4H, m, 2 × C**5**-H, 2 × C**6**-H), 2.60 (1H, m, C**2**-H), 0.75 (2H, m, 2 × C**1**-H), 0.51 (2H, m, 2 × C**1**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.9 (C**3**), 144.6 (C**8**), 127.0, 119.4 (C**5**, C**6**), 23.3 (C**2**), 7.3 (C**1**); HRMS: (ESI^+) Calculated for $C_{11}H_{11}F_3N_2NaO$: 267.0716. Found $[M + Na]^+$: 267.0714.

3-(4-(Trifluoromethyl)phenyl)-1,3-diazepane-2,4-dione (204f) ***and*** **1-(4-(Trifluoromethyl) phenyl)-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (203f)**



202f **203f** **204f**

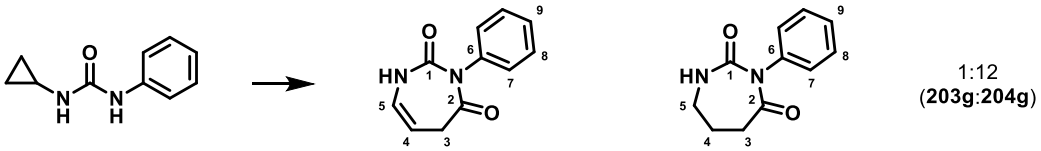
General Procedure B: Urea **202f** (36.6 mg, 0.150 mmol) and $[Rh(cod)_2]$BARF (5.0 mol%) were employed, and the reaction was stirred for 42 h at 90 °C. The crude mixture was purified by FCC (30% EtOAc/hexane) to yield the title compound **204f** (29.1 mg, 71%, 3:1 **204f**:**203f**) as a yellow solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 3:1 (**204f**:**203f**) mixture of products. **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 3131 (br.), 3075 (br.), 1707 (s), 1692 (s), 1602 (m), 1557 (m), 1325 (m), 1112 (s). **Data for major compound 204f:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.80 (1H, br. s, NH), 7.72–7.54 (4H, m, 2 × C**7**-H, 2 × C**8**-H), 3.96 (2H, t, *J* = 7.0 Hz, C**5**-H_2), 2.71 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.11 (2H, tt, *J* = 8.0, 7.0 Hz, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.7 (C**2**), 126.4, 119.7 (C**7**, C**8**), 45.8 (C**5**), 33.6 (C**3**), 16.9 (C**4**); HRMS: (ESI^+) Calculated for $C_{12}H_{11}F_3N_2NaO_2$: 295.0665. Found $[M + Na]^+$: 295.0659. **Data for minor compound 203f:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.70 (1H, br. s, NH), 7.72–7.54 (4H, m, 2 × C**7**-H, 2 × C**8**-H), 7.40 (1H, dt, *J* = 6.0, 2.0 Hz, C**5**-H), 6.29 (1H, dt, *J* = 6.0, 2.0 Hz, C**4**-H), 4.56 (2H, dd, *J* = 2.0, 2.0 Hz, C**3**-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.0 (C**2**), 147.3 (C**5**), 127.2 (C**4**), 126.4, 119.7 (C**7**, C**8**), 51.4 (C**3**).

1-Cyclopropyl-3-phenylurea (202g)

202g

General procedure A: Cyclopropylamine (0.760 mL, 11.0 mmol) and phenyl isocyanate (0.900 mL, 10.0 mmol) were employed to yield the title compound **202g** (1.30 g, 74%) as a colourless solid; m.p. 160–161 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3341 (w), 1642 (s), 1594 (s), 1547 (s), 1242 (s), 741 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38 (2H, m, 2 × C**5**-H), 7.29 (2H, m, 2 × C**6**-H), 7.07 (1H, br. s, NH), 7.05 (1H, m, C**7**-H), 5.17 (1H, br. s, NH), 2.59 (1H, m, C**2**-H), 0.81 (2H, m, 2 × C**1**-H), 0.62 (2H, m, 2 × C**1**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.8 (C**3**), 138.7 (C**4**), 129.2 (C**6**), 123.5 (C**7**), 120.2 (C**5**), 22.7 (C**2**), 7.6 (C**1**); HRMS: (ESI^+) Calculated for $C_{10}H_{12}N_2NaO$: 199.0842. Found $[M + Na]^+$: 199.0847.

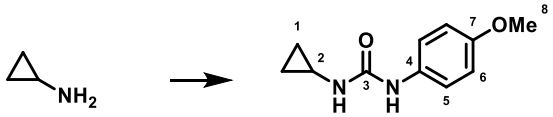
3-Phenyl-1,3-diazepane-2,4-dione (204g) ***and*** **1-Phenyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (203g)**



202g **203g** **204g**

General Procedure B: Urea **202g** (26.4 mg, 0.150 mmol) and $[Rh(cod)_2]BARF$ (5.0 mol%) were employed with 1,4-dioxane as solvent, and the reaction was stirred for 49 h at 90 °C. The crude mixture was purified by FCC (25% EtOAc/hexane) to yield the title compound **204g** (20.5 mg**,** 67%, 25:1, **204g**:**203g**) as a beige solid. Analysis of the crude reaction mixture by ^1H NMR revealed a 12:1 (**204g**:**203g**) mixture of products. The minor product **203g** was not isolated. **Data for the major product 204g:** m.p. 89–92 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3088 (m), 1719 (s), 1599 (s), 1556 (s), 1379 (s), 1210 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 10.54 (1H, br. s, NH), 7.53 (2H, m, 2 × C**8**-H), 7.33 (2H, m, 2 × C**7**-H), 7.10 (1H, t, C**9**-H), 3.95 (2H, t, *J* = 7.2 Hz, C**5**-H_2), 2.69 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.09 (2H, dt, *J* = 8.0, 7.0 Hz, C**4**-H_2); ^{13}C ($CDCl_3$, 100 MHz): δ 177.3 (C**2**), 150.1 (C**1**), 137.4 (C**7**), 129.0 (C**8**), 124.0 (C**10**), 120.0 (C**9**), 45.7, 33.5 (C**3**, C**5**), 16.8 (C**4**). HRMS: (ESI^+) Calculated for $C_{11}H_{12}N_2NaO_2$: 227.0791. Found $[M + Na]^+$: 227.0791. **Data for the minor product 203g:** *Characteristic signals only*: ^1H NMR ($CDCl_3$, 400 MHz): δ 6.25 (1H, dt, *J* = 6.0, 2.0 Hz, C**4**-H).

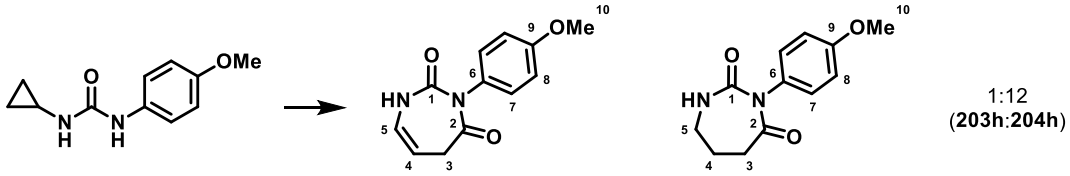
1-Cyclopropyl-3-(4-methoxyphenyl)urea (202h)



202h

General procedure A: Cyclopropylamine (0.760 mL, 11.0 mmol) and 1-isocyanato-4-methoxybenzene (1.09 mL, 10.0 mmol) were employed to yield the title compound **202h** (1.98 g, 96%) as a colourless solid; m.p. 146–149 °C (CH_2Cl_2); ν_{max} / cm^{-1}: 3289 (m), 1637 (s), 1561 (s), 1508 (s), 1243 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 (2H, m, 2 × C**6**-H), 6.86 (2H, m, 2 × C**5**-H), 6.68 (1H, br. s, NH), 3.79 (3H, s, C**8**-H_3), 2.58 (1H, m, C**2**-H), 0.81 (2H, m, 2 × C**1**-H), 0.63 (2H, m, 2 × C**1**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5 (C**7**), 131.3 (C**4**), 123.3 (C**6**), 114.5 (C**5**), 55.6 (C**8**), 22.8 (C**2**), 7.78 (C**1**); HRMS: (ESI^+) Calculated for $C_{11}H_{14}N_2NaO$: 229.0953. Found $[M + Na]^+$: 229.0947.

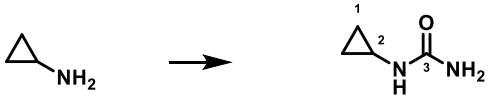
3-(4-Methoxyphenyl)-1,3-diazepane-2,4-dione (204h) ***and*** **1-(4-Methoxyphenyl)-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (203h)**



202h **203h** **204h**

General Procedure B: Urea **202h** (30.9 mg, 0.150 mmol) and $[Rh(cod)_2]$BARF (5.0 mol%) were employed, and the reaction was stirred for 25 h at 90 °C. The crude mixture was purified by FCC (30% EtOAc/hexane) to yield the title compound **204h** (22.0 mg**,** 63%) as a colourless solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 12:1 (**204h**:**203h**) mixture of products. The minor product **203h** was not isolated. **Data for major compound 204h:** m.p. 114–116 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 2918 (m), 1702 (s), 1552 (s), 1511 (s), 1382 (s), 1212 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.4 (1H, br. s, NH), 7.42 (2H, m, 2 × C**8**-H), 6.86 (2H, m, 2 × C**7**-H), 3.94 (2H, t, *J* = 7.0 Hz, C**5**-H_2), 3.78 (3H, s, C**10**-H_3), 2.68 (2H, t, *J* = 8.0 Hz, C**3**-H_2), 2.07 (2H, tt, *J* = 8.0, 7.0 Hz, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.3 (C**2**), 156.4 (C**9**), 150.5 (C**1**), 130.6 (C**6**), 121.9 (C**8**), 114.3 (C**7**), 55.6 (C**10**), 45.8 (C**5**), 33.7 (C**3**), 16.9 (C**4**); HRMS: (ESI^+) Calculated for $C_{12}H_{14}N_2NaO_3$: 257.0902. Found $[M + Na]^+$: 257.08967. **Data for the minor product 203h:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.25 (1H, d, *J* = 6.0 Hz, C**4**-H).

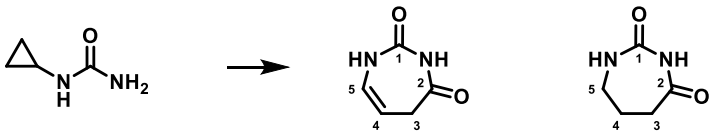
1-Cyclopropylurea (202i)



202i

Cyclopropylamine (4.85 mL, 70.0 mmol) was added to 5 M aq. HCl (14 mL), dropwise at 0 °C followed by potassium cyanate (5.65 g, 69.0 mmol). The reaction mixture was then heated at 70 °C for 20 h before being cooled to room temperature and concentrated *in vacuo*. The resulting colourless solid was dissolved in water (250 mL) and the pH was adjusted to neutral. The aqueous solution was then extracted with EtOAc (3 × 100 mL). The combined organics were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* affording the title compound **202i** (273 mg, 4%) as a colourless solid; m.p. 122–124 °C (MeOH); ν_{max} / cm^{-1}: 3421 (m), 3332 (m), 1652 (s), 1602 (s), 1551 (s), 1340 (s); ^{1}H NMR (400 MHz, MeOD-d4): δ 2.46 (1H, m, C**2**-H), 0.70 (2H, m, 2 × C**1**-H$_2$), 0.47 (2H, m, 2 × C**1**-H$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5 (C**3**), 23.4 (C**2**), 7.3 (C**1**); *m/z* (ESI^+) HRMS: Calculated for $C_4H_8N_2NaO$: 123.0534. Found $[M + Na]^+$: 123.0528.

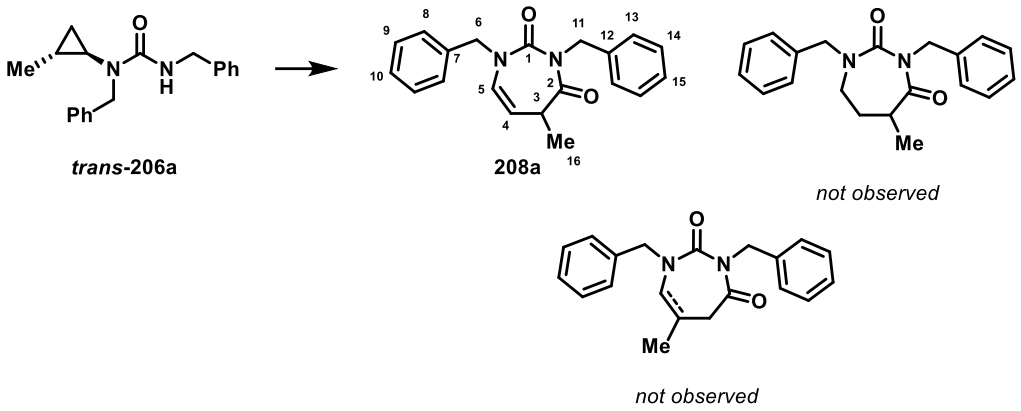
3,6-Dihydro-1*H*-1,3-diazepine-2,7-dione (203i)



202i **203i** **204i**
not observed

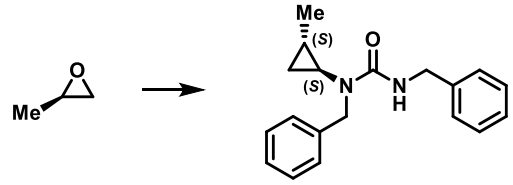
General Procedure B: Urea **202i** (15.0 mg, 0.150 mmol) and $Rh(cod)_2BARF$ (5.0 mol%) were employed, and the reaction was stirred for 72 h at 100 °C. The crude mixture was filtered, washing with Et_2O, to yield the title compound **203i** (10.4 mg**,** 55%) as a brown solid; m.p. 185–187 °C (MeOH); ν_{max} / cm^{-1}: 3220 (m), 3083 (m), 2960 (m), 1694 (s), 1659 (s), 1427 (m), 1384 (s), 1287 (s), 1121 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (1H, d, *J* = 7.5 Hz, C**5**-H), 5.31 (1H, dd, *J* = 7.5, 7.0 Hz, C**4**-H), 3.11 (2H, d, *J* = 7.0 Hz, C**3**-H$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2 (C**2**), 172.7 (C**1**), 127.7 (C**5**), 108.3 (C**4**), 35.3 (C**3**); *m/z* (ESI^+) HRMS: Calculated for $C_5H_6N_2NaO_2$: 149.0321. Found $[M + Na]^+$: 149.0327.

1,3-Dibenzyl-6-methyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (208a)



General Procedure B: *Urea **trans-206a** was synthesised by McCreanor*[103]: Urea ***trans*-206a** (44.2 mg, 0.150 mmol) and $[Rh(cod)_2]BARF$ (7.5 mol%) were employed, and the reaction was stirred for 73 h at 100 °C. The crude mixture was purified by FCC (10% EtOAc/hexane) to yield the title compound **208a** (33.5 mg, 70%) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed complete selectivity for **208a** over the corresponding saturated product and C4-substituted regioisomer. ν_{max} / cm^{-1}: 2987 (m), 1699 (s), 1649 (s), 1402 (s), 1265 (s), 1183 (s), 1076 (s), 1046 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.22 (8H, m, 2 × C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 7.07–7.02 (2H, m, 2 × C**8**-H), 5.99 (1H, dd, *J* = 7.0 Hz, 2.0 Hz, C**5**-H), 5.27 (1H, d, *J* = 14.5 Hz, 1 × C**11**-H), 5.21 (1H, dd, *J* = 7.0, 6.0 Hz, C**4**-H), 4.90 (1H, d, *J* = 14.5 Hz, 1 × C**11**-H), 4.83 (1H, d, *J* = 15.0 Hz, 1 × C**6**-H), 4.66 (1H, d, *J* = 15.0 Hz, 1 × C**6**-H), 3.06 (1H, qdd, *J* = 7.0, 6.0, 2.0 Hz, C**3**-H), 1.35 (3H, d, *J* = 7.0 Hz, C**16**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3 (C**2**), 154.0 (C**1**), 137.7 (C**12**), 136.1 (C**7**), 128.7, 128.5, 128.4, 128.1, 127.7, 127.6, 127.2 (C**5**, C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 120.2 (C**4**), 52.9 (C**6**), 48.2 (C**11**), 38.0 (C**3**), 13.7 (C**16**); HRMS: (ESI^+) Calculated for $C_{20}H_{20}N_2NaO_2$: 343.1417. Found $[M + Na]^+$: 343.1413.

1,3-Dibenzyl-1-((1*S*,2*S*)-2-methylcyclopropyl)urea ((*S*,*S*)-206a)



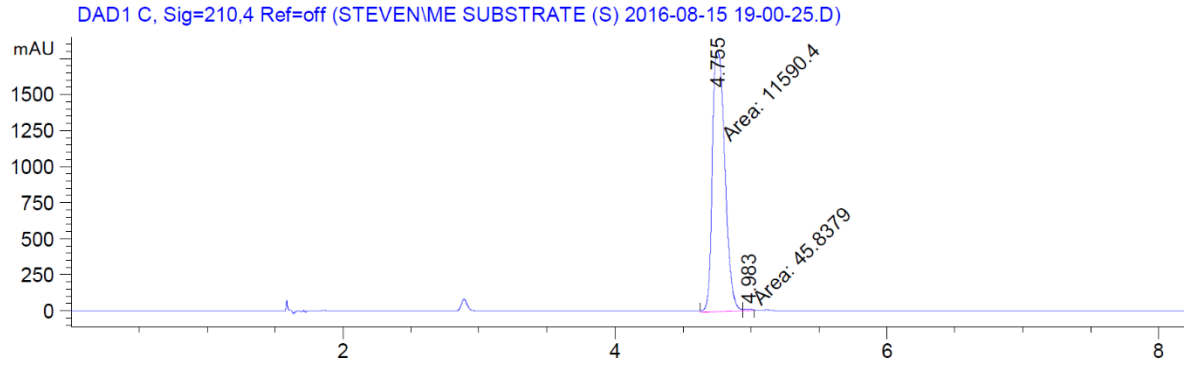
(*R*)-propylene oxide
commercially available

(*S*,*S*)-206a
99% ee

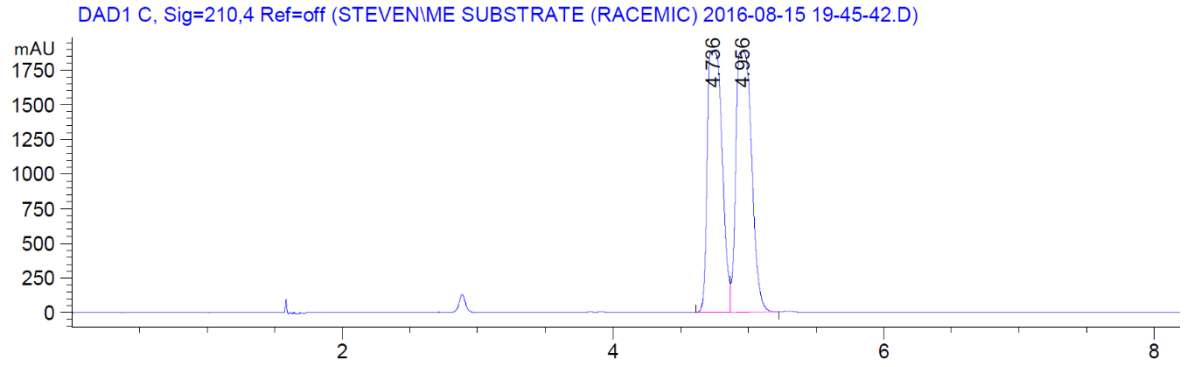
Enantiopure substrate **(*S*,*S*)-206a** (99% e.e.) was synthesised starting from the commercially available and (*R*)-propylene oxide according to the literature procedure.[101, 154]

Data for enantioenriched (*S*,*S*)-206a: $[\alpha]_D^{27}$ +41.1 (c = 1.2, $CHCl_3$).

The enantiopurity of this compound was determined by chiral SFC (Chiralpak IB, isocratic CO_2-MeOH 88:12, 2.0 mL/min, 40 °C) against a racemic standard; t_R (major) – 4.8 min and t_R (minor) – 5.0 min.

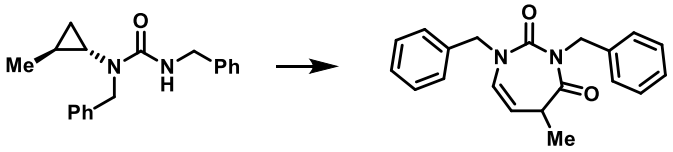


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.755	MF	0.1068	1.15904e4	1809.53076	99.6061
2	4.983	FM	0.0680	45.83789	11.22983	0.3939



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.736	BV	0.0902	1.43725e4	1889.92505	48.4774
2	4.956	VB	0.0965	1.52754e4	1885.69458	51.5226

(*S*)-1,3-Dibenzyl-6-methyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione ((*S*)-208a)



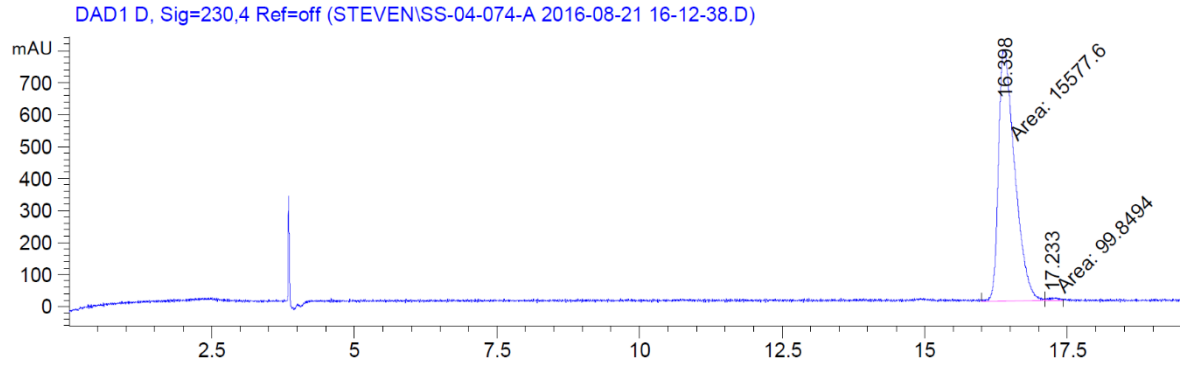
(*S*,*S*)-206a
99% e.e.

(*S*)-208a
99% e.e.

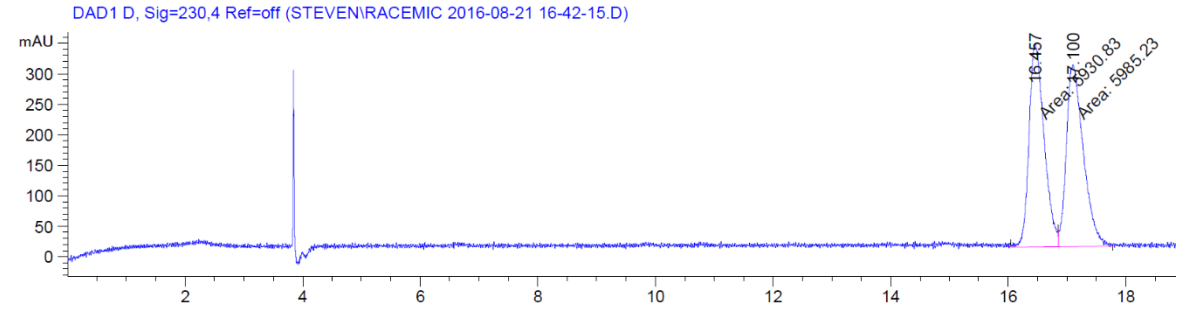
General Procedure B: Urea **(*S*,*S*)-206a** (44.2 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (7.5 mol%) were employed, and the reaction was stirred for 74 h at 100 °C. The crude mixture was purified by FCC (10% EtOAc/hexane) to yield the title compound **(*S*)-208a** (21.1 mg, 65%, 99% e.e.) as a yellow oil.

Data for enantioenriched (*S*)-206a: $[\alpha]_D^{27}$ +205.2 (c = 1.2, $CHCl_3$).

The enantiopurity of this compound was determined by chiral SFC (Chiralpak IB, isocratic CO_2-MeOH 95:5, 1.0 mL/min, 8 °C) against a racemic standard; t_R (major – 16.4 min and t_R (minor) – 17.2 min.

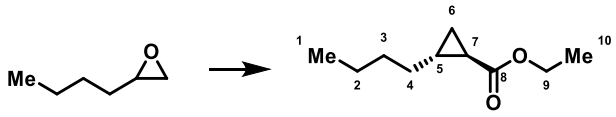


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.398	MF	0.3310	1.55776e4	784.31073	99.3631
2	17.233	FM	0.1726	99.84943	9.64204	0.6369



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.457	MF	0.2961	5930.83105	333.84116	49.7717
2	17.100	FM	0.3346	5985.22900	298.11276	50.2283

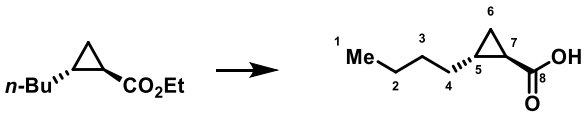
Ethyl (1*R,2*R**)-2-butylcyclopropane-1-carboxylate (211b)**



211b

This procedure was carried out in 6 identical reaction tubes in parallel. To a flame-dried screw-top tube, fitted with a rubber septum under an atmosphere of nitrogen was added 1,2-dimethoxyethane (11 mL) and triethyl phosphonoacetate (1.11 mL, 5.60 mmol). The reaction tube was then placed in an ice bath before the dropwise addition of *n*-BuLi (3.68 mL, 1.6 M in hexanes, 5.88 mmol). 2-Butyloxirane (0.337 mL, 2.80 mmol) was then added and the reaction tube was sealed and heated at 130 °C for 18 h before cooling to room temperature. *The 6 identical reactions were combined at this point*. The reaction mixture was transferred to a separating funnel with Et_2O (50 mL) and sat. aq. NH_4Cl (120 mL). The layers were separated and the aqueous layer was further extracted with Et_2O (3 × 50 mL). The combined organics were dried over Mg_2SO_4 and concentrated *in vacuo*. Purification by FCC (5% EtOAc/Hexane) provided the title compound (2.86 g, 94%) as a pale yellow oil; ν_{max} / cm^{-1}: 2925 (m), 1725 (s), 1449 (m), 1337 (m), 1264 (m), 1203 (m), 1176 (s), 1038 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (2H, q, *J* = 7.0 Hz, C**9**-$\underline{H}_2$), 1.43–1.22 (8H, m, C**2**-$\underline{H}_2$, C**3**-$\underline{H}_2$, C**4**-$\underline{H}_2$, C**5**-$\underline{H}$, C**7**-$\underline{H}$), 1.25 (3H, t, *J* = 7.0 Hz, C**10**-$\underline{H}_3$), 1.14 (1H, m, 1 × C**6**-$\underline{H}_2$), 0.89 (3H, t, *J* = 7.0 Hz, C**1**-$\underline{H}_3$), 0.68 (1H, m, 1 × C**6**-$\underline{H}_2$). *The spectroscopic properties of this compound were consistent with that available in the literature*.[356]

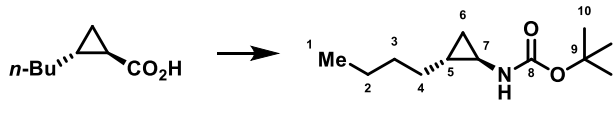
(1*R,2*R**)-2-Butylcyclopropane-1-carboxylic acid (*trans*-212b)**



211b **trans-212b**

General procedure C: Ester **211b** (2.70 g, 15.9 mmol) was employed to provide the title compound ***trans*-212b** (832 mg, 37%) as a yellow oil; ν_{max} / cm^{-1}: 1687 (s), 1457 (m), 1431 (m), 1229 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47–1.19 (9H, m, 2 × C**7**-$\underline{H}_2$, 2 × C**6**-$\underline{H}_2$, 2 × C**5**-$\underline{H}_2$, C**4**-$\underline{H}$, C**2**-$\underline{H}$, 1 × C**6**-$\underline{H}_2$), 0.89 (3H, t, *J* = 7.0 Hz, 3 × C**8**-$\underline{H}_3$), 0.77 (1H, ddd, *J* = 8.0, 6.5, 4.0 Hz, 1 × C**6**-$\underline{H}_2$). *The spectroscopic properties of this compound were consistent with that available in the literature*.[357]

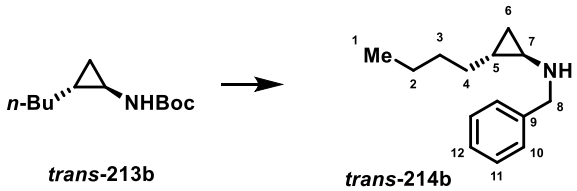
***tert*-Butyl ((1*R**,2*R**)-2-butylcyclopropyl)carbamate (*trans*-213b)**



trans-212b **trans-213b**

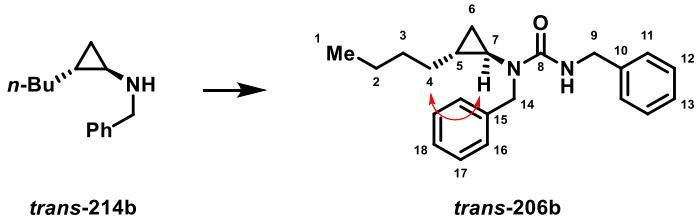
General procedure D: Carboxylic acid ***trans*-212b** (1.34 g, 9.39 mmol) was employed and the reaction was stirred for 3.5 h. The crude mixture was purified by FCC (5% EtOAc/hexane) to yield the title compound **66** (976 mg, 49%) as a colourless oil; ν_{max} / cm^{-1}: 3329 (m), 2924 (m), 1693 (s), 1517 (m), 1390 (m), 1365 (s), 1250 (m), 1170 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.65 (1H, br. s, NH), 2.23 (1H, m, C**7**-H), 1.44 (9H, s, 3 × C**10**-H_3), 1.41–1.27 (5H, m, C**2**-H_2, C**3**-H_2, 1 × C**4**-H_2), 1.13 (1H, m, 1 × C**4**-H_2), 0.88 (3H, t, *J* = 7.1 Hz, C**1**-H_3), 0.80 (1H, m, C**5**-H), 0.59 (1H, m, 1 × C**6**-H_2), 0.48 (1H, m, 1 × C**6**-H_2). *The spectroscopic properties of this compound were consistent with that available in the literature*.[102]

(1*R,2*R**)-*N*-Benzyl-2-butylcyclopropan-1-amine (*trans*-214b)**



General procedure E: Boc-protected amine ***trans*-213b** (549 mg, 2.57 mmol) was employed and the residue was purified by FCC (15% EtOAc/hexane) to provide the title product (511 mg, 98%) as an orange oil; ν_{max} / cm^{-1}: 3293 (br.), 2955 (m), 2921 (m), 1646 (m), 1547 (m), 1453 (s), 1025 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.22 (5H, m, 2 × C**10**-H, 2 × C**11**-H, C**12**-H), 3.82 (2H, s, C**8**-H_2), 1.87 (1H, m, C**7**-H), 1.75 (1H, br. s, NH), 1.38–1.26 (4H, m, C**2**-H_2, C**3**-H_2), 1.21–1.11 (2H, m, C**4**-H_2), 0.88 (3H, t, *J* = 7.0 Hz, C**1**-H_3), 0.74 (1H, m, C**5**-H), 0.54 (1H, m, 1 × C**6**-H_2), 0.24 (1H, m, 1 × C**6**-H_2). *The spectroscopic properties of this compound were consistent with that available in the literature*.[102]

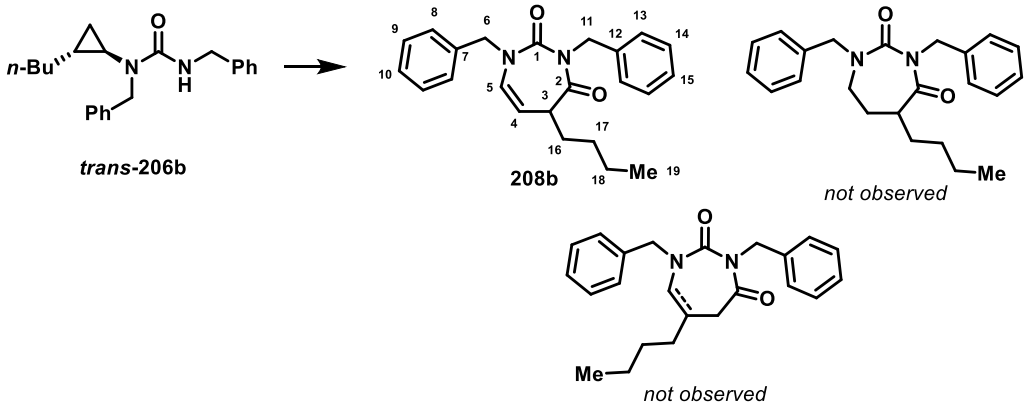
1,3-Dibenzyl-1-((1*R,2*R**)-2-butylcyclopropyl)urea (*trans*-206b)**



General procedure A: Amine ***trans*-214b** (497 mg, 2.44 mmol) was employed and the residue was purified by FCC (20% EtOAc/hexane) to provide the title compound (677 mg, 82%) as a colourless oil; ν_{max} / cm^{-1}: 2956 (m), 2923 (m), 1644 (s), 1513 (s), 1453 (m), 1352 (m), 1267 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.21 (10H, m, 2 × C**11**-H, 2 × C**12**-H, C**13**-H, 2 × C**16**-H, 2 × C**17**-H, C**18**-H), 5.52 (1H, m, NH), 4.57 (2H, s, C**14**-H_2), 4.50 (2H, t, *J* = 5.0 Hz, C**9**-H_2), 2.08 (1H, m, C**7**-H), 1.26–1.17 (5H, m, 2 × C**2**-H, 2 × C**3**-H, 1 × C**4**-H), 1.12–1.01 (2H, m, 1 × C**4**-H, 1 × C**5**-H), 0.87 (1H, m, 1 × C**6**-H), 0.81 (3H, m, C**1**-H_3), 0.55 (1H, m, 1 × C**6**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0 (C**8**), 139.8 (C**10**), 139.2 (C**15**), 128.8, 128.5, 127.9, 127.7, 127.4, 127.0 (C**11**, C**12**, C**13**, C**16**, C**17**, C**18**), 50.5

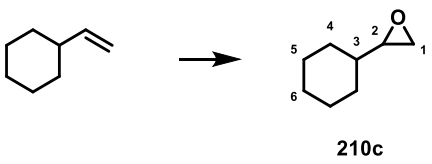
(C**14**), 45.0 (C**9**), 34.5 (C**7**), 32.1 (C**4**), 31.1, 22.6 (C**2**, C**3**), 22.4 (C**5**), 15.8 (C**6**), 14.0 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{22}H_{28}N_2NaO$: 359.2094. Found [M + Na]$^+$: 359.2094. *The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C**7**-H and C**4**-H$_2$. No significant nOe was observed between C**7**-H and C**5**-H.*

1,3-Dibenzyl-6-butyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (208b)



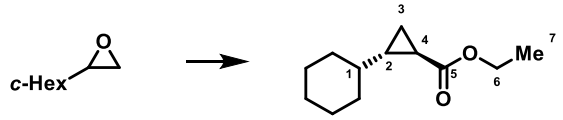
General Procedure B: Urea ***trans*-206b** (50.5 mg, 0.150 mmol) and [Rh(cod)$_2$]BF$_4$ (10 mol%) were employed, and the reaction was stirred for 45 h at 100 °C. The crude mixture was purified by FCC (7.5% EtOAc/hexane) to yield the title compound **208b** (32.2 mg, 59%) as a yellow solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed complete selectivity for **208b** over the corresponding saturated product and C4-substituted regioisomer; m.p. 88–89 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 2954 (m), 1688 (s), 1646 (s), 1446 (m), 1405 (s), 1332 (m), 1272 (m), 1181 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.21 (8H, m, 2 × C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 7.06–7.03 (2H, m, 2 × C**8**-H), 6.01 (1H, dd, *J* = 7.0, 2.0 Hz, C**5**-H), 5.26–5.23 (2H, m, C**4**-H, 1 × C**11**-H), 4.90 (1H, d, *J* = 14.5 Hz, 1 × C**11**-H), 4.81 (1H, d, *J* = 15.0 Hz, 1 × C**6**-H), 4.68 (1H, d, *J* = 15.0 Hz, 1 × C**6**-H), 2.89 (1H, m, C**3**-H), 1.96 (1H, m, 1 × C**16**-H), 1.64 (1H, m, 1 × C**16**-H), 1.33–1.25 (4H, m, 2 × C**17**-H, 2 × C**18**-H), 0.89 (3H, m, C**19**-H$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.8 (C**2**), 154.2 (C**1**), 137.9 (C**12**), 136.3 (C**7**), 129.0, 128.8, 128.5, 128.2, 127.9, 127.7, 127.3 (C**5**, C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 119.7 (C**4**), 22.9 (C**6**), 48.2 (C**11**), 43.7 (C**3**), 29.3 (C**17**), 27.9 (C**16**), 22.5 (C**18**), 14.1 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{23}H_{26}N_2NaO_2$: 385.1886. Found [M + Na]$^+$: 385.1891.

2-Cyclohexyloxirane (210c)



m-CPBA (2.93 g, 17.0 mmol) was added to a stirring solution of vinylcyclohexane (1.37 mL, 10.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 18 h during which time a white precipitate formed. The reaction mixture was transferred to a separating funnel with CH_2Cl_2 (40 mL) and sat. aq. Na_2SO_3 (50 mL). The phases were separated, and the organic layer was washed with sat. aq. $NaHCO_3$ (2 × 50 mL) and brine (50 mL) then concentrated *in vacuo* to provide the title compound (947 mg, 75%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72–2.68 (2H, m, 1 × C**1**-$\underline{H}_2$, C**2**-$\underline{H}$), 2.52 (1H, m, 1 × C**1**-$\underline{H}_2$), 1.89–1.64 (5H, m, 5 × cyclohexyl C$\underline{H}$), 1.29–1.04 (6H, m, 6 × cyclohexyl C$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.8 (C**2**), 46.1 (C**1**), 40.5 (C**3**), 29.9, 29.0, 26.5, 25.8, 25.7 (5 × cyclohexyl C$\underline{H}_2$). *The spectroscopic properties of this compound were consistent with that available in the literature*.[358]

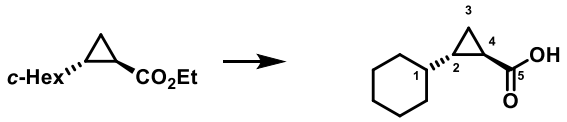
Ethyl (1*R,2*S**)-2-cyclohexylcyclopropane-1-carboxylate (211c)**



210c **211c**

This procedure was carried out in 3 identical reaction tubes in parallel. To a flame-dried sealable tube, fitted with a rubber septum, under an atmosphere of nitrogen was added 1,2-dimethoxyethane (5.0 mL) and triethyl phosphonoacetate (0.990 mL, 5.00 mmol). The reaction tube was then placed in an ice bath before the dropwise addition of *n*-BuLi (3.27 mL, 1.6 M in hexanes, 5.25 mmol). 2-Cyclohexyloxirane **210c** (316 mg, 2.50 mmol) was then added and the reaction tube was sealed and heated at 130 °C for 18 h before cooling to room temperature. *The 3 identical reactions were combined at this point*. The reaction mixture was transferred to a separating funnel with Et_2O (20 mL) and sat. aq. NH_4Cl (20 mL). The layers were separated, and the aqueous layer was further extracted with Et_2O (3 × 20 mL). The combined organics were dried over Mg_2SO_4 and concentrated *in vacuo*. Purification by FCC (5% EtOAc/hexane) provided the title compound (1.16 g, 79%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (2H, qd, *J* = 7.1 Hz, 2.0 Hz, C**6**-$\underline{H}_2$), 1.78–1.59 (5H, m, 5 × cyclohexyl C$\underline{H}$), 1.38 (1H, ddd, *J* = 8.2 Hz, 4.5 Hz, 4.1 Hz, C**4**-$\underline{H}$), 1.27–1.03 (7H, m, 5 × cyclohexyl C$\underline{H}$, C**2**-$\underline{H}$, C**3**-$\underline{H}$), 1.25 (3H, t, *J* = 7.1 Hz, C**7**-$\underline{H}_3$), 0.74–0.62 (2H, m, C**1**-$\underline{H}$, C**3**-$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9 (C**5**), 60.4 (C**6**), 41.8 (C**1**), 32.8, 32.6 (2 × cyclohexyl C$\underline{H}_2$), 29.5 (C**2**), 26.5, 26.3, 26.2 (3 × cyclohexyl C$\underline{H}_2$), 19.1 (C**4**), 14.4, 14.3 (C**3** and C**7**); *The spectroscopic properties of this compound were consistent with that available in the literature*.[101]

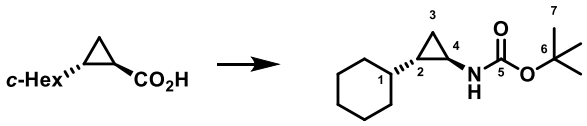
(1*R,2*S**)-2-Cyclohexylcyclopropane-1-carboxylic acid (*trans*-212c)**



211c ***trans*-212c**

General procedure C: Ester **211c** (1.16 g, 5.89 mmol) was employed to provide the title compound (844 mg, 85%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78–1.62 (5H, m, 5 × cyclohexyl C<u>H</u>), 1.39 (1H, ddd, *J* = 8.5, 4.5, 4.5 Hz, C**2**-<u>H</u>), 1.30 (1H, m, C**4**-<u>H</u>), 1.20–1.03 (6H, m, 1 × C**3**-<u>H</u>$_2$, 5 × cyclohexyl C<u>H</u>), 0.81 (1H, m, 1 × C**3**-<u>H</u>), 0.70 (1H, m, C**5**-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.0 (C**1**), 41.8 (C**5**), 32.7, 32.6 (2 × cyclohexyl <u>C</u>H), 30.6 (C**4**), 26.5, 26.2, 26.2 (3 × cyclohexyl <u>C</u>H), 18.9 (C**2**), 15.2 (C**3**); *The spectroscopic properties of this compound were consistent with that available in the literature*.[101]

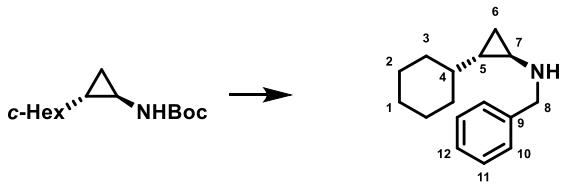
***tert*-Butyl ((1*R**,2*S**)-2-cyclohexylcyclopropyl)carbamate (*trans*-213c)**



***trans*-212c** ***trans*-213c**

General procedure D: Carboxylic acid ***trans*-212c** (800 mg, 4.76 mmol) was employed and the reaction was stirred for 17 h. The crude mixture was purified by FCC (5% EtOAc/hexane) to yield the title compound (975 mg, 86%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.62 (1H, br. s, N<u>H</u>), 2.28 (1H, m, C**4**-<u>H</u>), 1.90 (1H, m, 1 × cyclohexyl C<u>H</u>), 1.69–1.61 (4H, m, 4 × cyclohexyl C<u>H</u>), 1.44 (9H, s, 9 × C**7**-<u>H</u>$_3$), 1.19–0.96 (5H, m, 5 × cyclohexyl C<u>H</u>), 0.69–0.49 (4H, m, C**1**-<u>H</u>, C**2**-<u>H</u> and C**3**-<u>H</u>$_2$); *The spectroscopic properties of this compound were consistent with that available in the literatur*e.[101]

(1*R,2*S**)-*N*-Benzyl-2-cyclohexylcyclopropan-1-amine (*trans*-214c)**

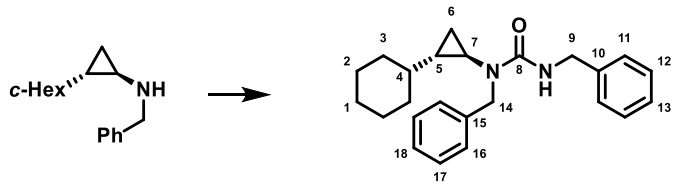


***trans*-213c** ***trans*-214c**

General procedure E: Boc-protected amine ***trans*-213c** (450 mg, 1.88 mmol) was employed and the residue was purified by FCC (10% EtOAc/hexane) to provide the title compound (375 mg, 87%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.22 (5H, m, 2 × C**10**-<u>H</u>, 2 × C**11**-<u>H</u>, C**12**-<u>H</u>), 3.81 (2H, s, C**8**-<u>H</u>$_2$), 1.93 (1H, ddd, *J* = 6.7, 3.2, 3.2 Hz, C**7**-<u>H</u>), 1.78–1.60 (5H, m, 5 × cyclohexyl C<u>H</u>), 1.22–0.97 (5H, m, 5 × cyclohexyl C<u>H</u>), 0.64–0.46 (3H, m, C**4**-<u>H</u>, C**5**-<u>H</u>, 1 × C**6**-<u>H</u>$_2$), 0.30 (1H, m, 1 × C**6**-<u>H</u>$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8 (C**9**), 128.5, 128.3, 126.9 (C**10**, C**11**, C**12**), 53.9 (C**8**), 41.1 (C**4**), 36.4 (C**7**), 33.2, 32.6 (2 × cyclohexyl $\underline{C}H_2$), 27.7 (C**5**), 26.7, 26.4 (3 × cyclohexyl $\underline{C}H_2$), 12.6 (C**6**); *The spectroscopic properties of this compound were consistent with that available in the literature*.[101]

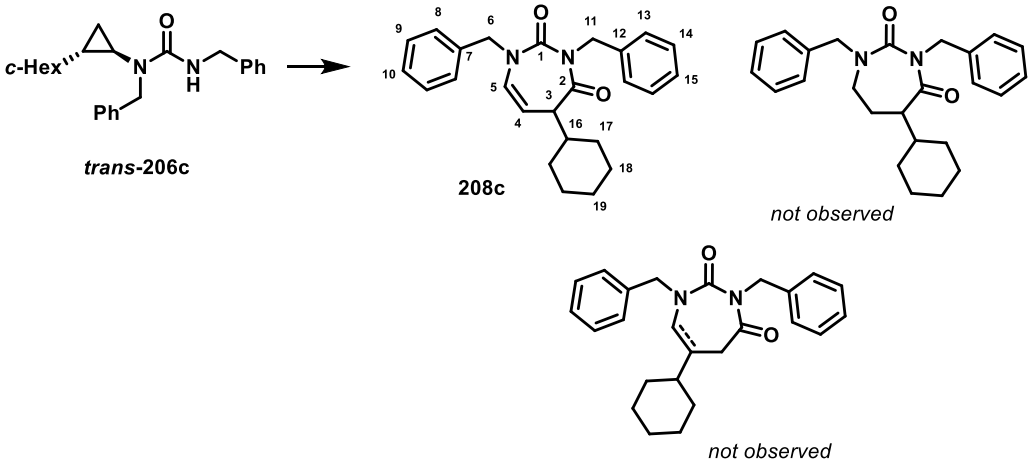
1,3-Dibenzyl-1-((1*R,2*S**)-2-cyclohexylcyclopropyl)urea (*trans*-206c)**



***trans*-214c** ***trans*-206c**

General procedure A: Amine ***trans*-214c** (355 mg, 1.55 mmol) was employed and the residue was purified by FCC (15–20% EtOAc/hexane) to provide the title compound (500 mg, 89%) as a colourless solid; m.p. 73–74 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3346 (m), 2922 (m), 1630 (s), 1518 (s), 1349 (m), 1221 (m), 696 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.21 (10H, m, 2 × C**11**-$\underline{H}$, 2 × C**12**-$\underline{H}$, C**13**-$\underline{H}$, 2 × C**16**-$\underline{H}$, 2 × C**17**-$\underline{H}$, C**18**-$\underline{H}$,), 5.63 (1H, t, *J* = 5.0 Hz, N$\underline{H}$), 4.64 (1H, d, *J* = 15.5 Hz, 1 × C**14**-$\underline{H}$), 4.51 (1H, d, *J* = 15.5 Hz, 1 × C**14**-$\underline{H}$), 4.49 (2H, m, C**9**-$\underline{H}_2$), 2.20 (1H, m, C**7**-$\underline{H}$), 1.68–1.50 (5H, m, 5 × cyclohexyl C$\underline{H}$), 1.13–0.88 (6H, m, C**4**-$\underline{H}$, 5 × cyclohexyl C$\underline{H}$), 0.82 (1H, m, 1 × C**6**-$\underline{H}$), 0.64–0.47 (2H, m, C**5**-$\underline{H}$, 1 × C**6**-$\underline{H}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0 (C**8**), 139.7 (C**10**), 139.4 (C**15**), 128.7, 128.5, 127.9, 127.7, 127.4, 126.9 (C**11**, C**12**, C**13**, C**16**, C**17**, C**18**), 50.7 (C**14**), 45.1 (C**9**), 41.0 (C**5**), 33.7 (C**7**), 32.7, 32.1 (2 × cyclohexyl $\underline{C}H_2$), 28.7 (C**4**), 26.3, 26.1, 26.1 (3 × cyclohexyl $\underline{C}H_2$), 14.7 (C**6**); HRMS: (ESI$^+$) Calculated for $C_{24}H_{30}N_2NaO$: 385.2256. Found [M + Na]$^+$: 385.2342.

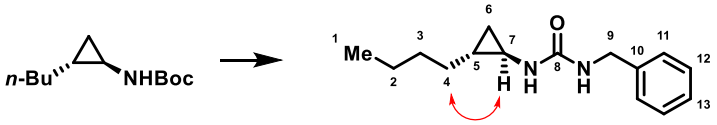
1,3-Dibenzyl-6-cyclohexyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (208c)



General Procedure B: Urea ***trans*-206c** (54.4 mg, 0.150 mmol) and $[Rh(cod)_2]BF_4$ (7.5 mol%) were employed, and the reaction was stirred for 73 h at 100 °C. The crude mixture was purified by FCC (7.5% EtOAc/hexane) to yield the title compound **208c** (16.9 mg, 29%) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed complete selectivity for **208c** over the corresponding

saturated product and C4-substituted regioisomer. ν_{max} / cm^{-1}: 2923 (m), 2850 (m), 1698 (m), 1646 (s), 1401 (s), 1178 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.21 (8H, m, 2 × C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 7.07–7.03 (2H, m, 2 × C**8**-H), 6.01 (1H, dd, *J* = 7.0, 1.5 Hz, C**5**-H), 5.38 (1H, dd, *J* = 7.0, 7.0 Hz, C**4**-H), 5.18 (1H, d, *J* = 14.5 Hz, 1 × C**11**-H), 4.92 (1H, d, *J* = 14.5 Hz, 1 × C**11**-H), 4.84 (1H, d, *J* = 15.0 Hz, 1 × C**6**-H), 4.63 (1H, d, *J* = 15.0 Hz, 1 × C**6**-H), 2.67 (1H, m, C**3**-H), 1.96–1.86 (2H, m, C**16**-H, 1 × C**17**-H), 1.79 (1H, m, 1 × cyclohexyl CH), 1.70–1.63 (3H, m, 3 × cyclohexyl CH), 1.34–1.08 (3H, m, 3 × cyclohexyl CH), 0.91–0.79 (2H, m, 1 × C**17**-H, 1 × cyclohexyl CH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.7 (C**2**), 154.2 (C**1**), 137.9 (C**12**), 136.2 (C**7**), 129.1 (C**5**), 128.8, 128.5, 128.2, 127.9, 127.8, 127.3 (C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 117.8 (C**4**), 52.9 (C**6**), 50.2 (C**3**), 48.3 (C**11**), 35.7 (C**16**), 31.9 (C**17**), 30.3, 26.5, 26.1, 25.9 (C**17**, 2 × C**18**, C**19**); HRMS: (ESI^+) Calculated for $C_{25}H_{28}N_2NaO_2$: 411.2043. Found $[M + Na]^+$: 411.2050.

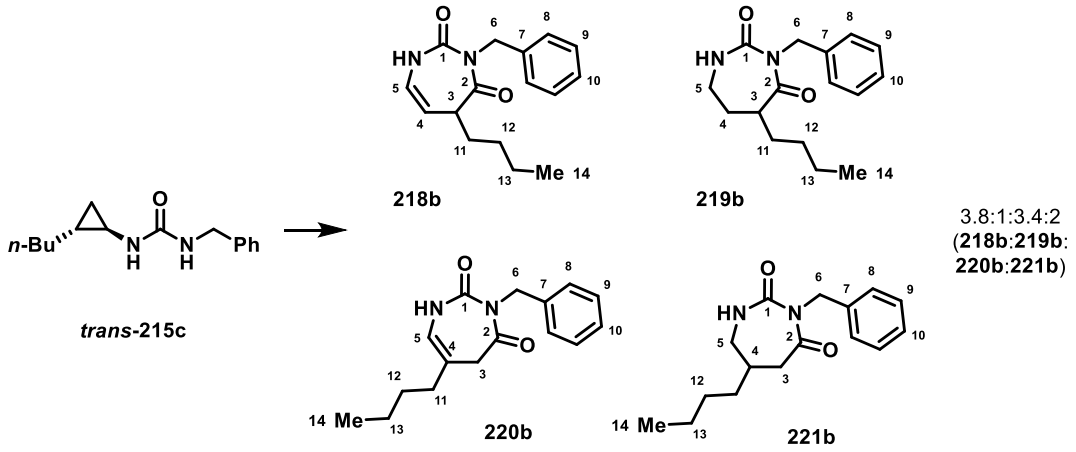
1-Benzyl-3-((1*R,2*R**)-2-butylcyclopropyl)urea (*trans*-215b)**



***trans*-213c** ***trans*-215c**

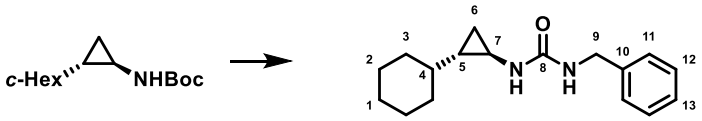
General procedure F: Boc-protected amine ***trans*-213b** (427 mg, 2.00 mmol) was employed and the residue was purified by FCC (40% EtOAc/hexane) to provide the title compound (463 mg, 94%) as a colourless solid; m.p. 80–83 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3318 (m), 2915 (m), 1625 (s), 1570 (s), 1454 (m), 1242 (s), 1067 (m), 696 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.23 (5H, m, 2 × C**11**-H, 2 × C**12**-H, C**13**-H), 5.23 (1H, br. m, NH), 4.74 (1H, br. s, NH), 4.43 (2H, m, C**9**-H_2), 2.14 (1H, m, C**7**-H), 1.35–1.16 (6H, m, 2 × C**2**-H, 2 × C**3**-H, 2 × C**4**-H), 0.94–0.82 (4H, m, C**1**-H_3, C**5**-H), 0.69 (1H, m, 1 × C**6**-H), 0.51 (1H, m, 1 × C**6**-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.0 (C**8**), 139.4 (C**10**), 128.8, 127.7, 127.4 (C**11**, C**12**), 127.4 (C**13**), 44.4 (C**9**), 32.0 (C**4**), 31.3 (C**3**), 29.1 (C**7**), 22.5 (C**2**), 21.5 (C**5**), 14.9 (C**6**), 14.1 (C**1**); HRMS: (ESI^+) Calculated for $C_{15}H_{22}N_2NaO$: 269.1624. Found $[M + Na]^+$: 269.1618. *The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C7-H to C4-H_2. No significant nOe was observed between C7-H and C5-H.*

1-Benzyl-5-butyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (218b), 3-Benzyl-5-butyl-1,3-diazepane-2,4-dione (219b), 1-Benzyl-6-butyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (220b) *and* 3-Benzyl-6-butyl-1,3-diazepane-2,4-dione (221b)



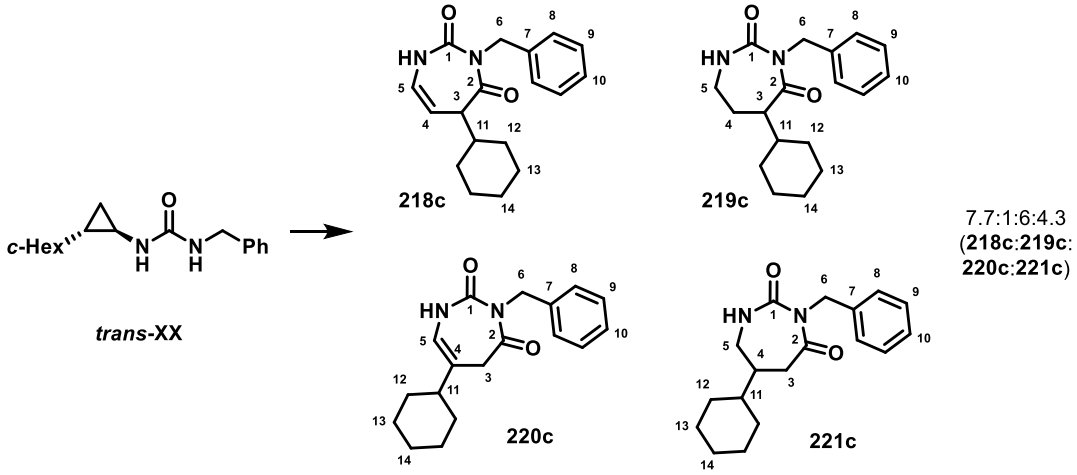
General Procedure B: Urea ***trans*-5v** (36.9 mg, 0.150 mmol) and $[Rh(cod)_2]BARF$ (5.0 mol%) were employed, and the reaction was stirred for 38 h at 100 °C. The crude mixture was purified by FCC (20% EtOAc/hexane) to yield the title compounds (28.8 mg, 70%, ~1:4:1:2, **218b**:**219b**:**220b**:**221b**) as a brown oil. **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 3298 (m), 2928 (m), 1705 (s), 1541 (s), 1361 (m), 1272 (m). **Data for product 218b:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.22 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 6.10 (1H, m, C**5**-H), 5.14 (1H, dd, *J* = 6.5, 6.5 Hz, C**4**-H), 5.07 (1H, d, J = 14.5 Hz, 1 × C**6**-H), 4.97 (1H, d, J = 14.5 Hz, 1 × C**6**-H), 3.05 (1H, m, C**3**-H), 2.00 (1H, m, 1 × C**11**-H), 0.96–0.89 (3H, m, C**14**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 124.6 (C**5**), 117.0 (C**4**), 48.3 (C**6**), 43.9 (C**3**), 28.4 (C**11**). **Data for product 219b:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.81 (1H, br. s, NH), 7.33–7.24 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 4.50 (2H, m, C**6**-H_2), 3.93 (1H, m, 1 × C**5**-H), 3.66 (1H, m, 1 × C**5**-H), 2.60 (1H, m, C**3**-H), 2.20 (1H, m, 1 × C**4**-H), 1.68 (1H, m, 1 × C**4**-H), 1.50–1.24 (6H, m, C**11**-H_2, C**12**-H_2, C**13**-H_2), 0.93–0.89 (3H, m, C**14**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.2 (C**2**), 44.4 (C**3**), 43.9, 43.9 (C**5**, C**6**), 24.1 (C**4**), 14.1 (C**14**); HRMS: (ESI^+) Calculated for $C_{16}H_{22}N_2NaO_2$: 297.1573. Found $[M + Na]^+$: 297.1583. **Data for product 220b:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.79 (1H, br. s, NH), 7.36–7.22 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 6.87 (1H, m, C**5**-H), 4.55 (2H, m, C**6**-H_2), 4.34 (2H, m, C**3**-H_2), 2.27 (2H, m, C**11**-H_2), 1.53 (2H, m, C**12**-H_2), 1.41–1.28 (2H, m, C**13**-H_2), 0.93 (3H, m, C**14**-H_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.3 (C**5**), 49.2 (C**3**), 43.9 (C**6**), 25.2 (C**11**). **Data for product 221b:** *Full characterisation data for compound **221b** is presented below.*

1-Benzyl-3-((1*R,2*S**)-2-cyclohexylcyclopropyl)urea (*trans*-215c)**



General procedure F: Boc-protected amine ***trans*-213c** (350 mg, 1.46 mmol) was employed and the residue was purified by FCC (40% EtOAc/hexane) to provide the title compound (345 mg, 87%) as a colourless solid; m.p. 80–83 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}:3319 (br.), 2919 (m), 2847 (m), 1626 (s), 1589 (s), 1577 (s), 1446 (m), 1255 (m), 1235 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.22 (5H, m, 2 × C**11**-H, 2 × C**12**-H, C**13**-H), 5.27 (1H, br. m, NH), 4.68 (1H, br. m, NH), 4.42 (2H, m, C**9**-H_2), 2.19 (1H, m, C**7**-H), 1.73–1.60 (5H, m, 5 × cyclohexyl CH), 1.18–0.94 (5H, m, 5 × cyclohexyl CH), 0.75 (1H, m, C**4**-H), 0.64 (1H, m, 1 × C**6**-H), 0.61–0.51 (2H, m, C**5**-H, 1 × C**6**-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.9 (C**8**), 139.3 (C**10**), 128.7, 127.8, 127.5 (C**11**, C**12**, C**13**), 44.5 (C**9**), 40.8 (C**5**), 32.9, 32.3 (2 × cyclohexyl CH_2), 28.2 (C**4**), 27.9 (C**7**), 26.4, 26.2, 26.1 (3 × cyclohexyl CH_2), 13.7 (C**6**); HRMS: (ESI^+) Calculated for $C_{17}H_{24}N_2NaO$: 295.1786. Found $[M + Na]^+$: 295.1775.

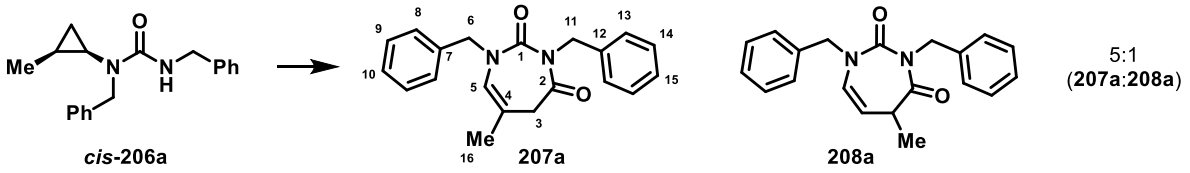
1-Benzyl-5-cyclohexyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (218c), 3-Benzyl-6-cyclohexyl-1,3-diazepane-2,4-dione (219c), 1-Benzyl-6-cyclohexyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (220c) *and* 3-Benzyl-5-cyclohexyl-1,3-diazepane-2,4-dione (221c),



General Procedure B: Compound ***trans*-215c** (40.8 mg, 0.150 mmol) and $[Rh(cod)_2]BARF$ (7.5 mol%) were employed, and the reaction was stirred for 72 h at 100 °C. The crude mixture was purified by FCC (25% EtOAc/hexane) to yield the title compounds (25.6 mg, 57%, 1:7.7:1:1.4, **218c**:**219c**:**220c**:**221c**) as a brown oil; *The compounds could not be separated by FCC. The products were assigned by analogy to* **218b**, **219b**, **220b**, **221b**. **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 3305 (br.), 2923 (m), 2853 (m), 1707 (s), 1537 (s), 1449 (m), 1360 (m), 1259 (m). **Data for product 218c:** *Characteristic signals only*: ^1H NMR ($CDCl_3$, 400 MHz): δ 6.09 (1H, m, C**5**-H), 5.27

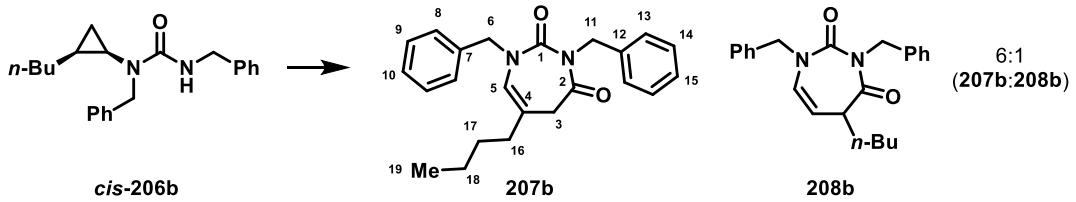
(1H, t, *J* = 7.0 Hz, C**4**-H). **Data for product 219c:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.87 (1H, m, 1 × C**5**-H), 3.66 (1H, m, 1 × C**5**-H); HRMS: (ESI^+) Calculated for $C_{18}H_{24}N_2NaO_2$: 323.1730. Found $[M + Na]^+$: 323.1739. **Data for product 220c:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.81 (1H, s, C**5**-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.8 (C**5**). **Data for product 221c:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.05 (1H, dd, *J* = 11.0, 8.0 Hz, 1 × C**5**-H), 3.43 (1H, dd, *J* = 11.0, 9.0 Hz, 1 × C**5**-H), 2.62 (1H, m, 1 × C**3**-H), 2.35 (1H, m, 1 × C**3**-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 49.8 (C**5**), 38.2 (C**3**).

1,3-Dibenzyl-5-methyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (207a) *and* 1,3- Dibenzyl-6-methyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (208a)



General Procedure B: *Urea **cis-206a** was synthesised by McCreanor*[103]: Urea ***cis*-206a** (44.2 mg, 0.150 mmol) and $[Rh(cod)_2]BARF$ (7.5 mol%) were employed, and the reaction was stirred for 72 h at 100 °C. The crude mixture was purified by FCC (25% EtOAc/hexane) to yield title compound **207a** (32.6 mg, 68%) as a pale yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 5:1 (**207a**:**208a**) mixture of products. **Data for major regioisomer 207a:** ν_{max} / cm^{-1}: 2971 (s), 1698 (s), 1646 (s), 1408 (s), 1214 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.21 (8H, m, 2 × C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 7.08–7.04 (2H, m, 2 × C**8**-H), 5.78 (1H, q, *J* = 1.5 Hz, C**5**-H), 5.04 (2H, s, C**11**-H_2), 4.71 (2H, s, C**6**-H_2), 3.04 (2H, s, C**3**-H_2), 1.86 (3H, s, C**16**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2 (C**2**), 154.1 (C**1**), 137.6 (C**12**), 136.3 (C**7**), 128.7, 128.4, 128.1, 127.7, 127.6, 127.2 (C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 124.5 (C**5**), 124.0 (C**4**), 52.9 (C**6**), 47.6 (C**11**), 40.8 (C**3**), 19.6 (C**16**); HRMS: (ESI^+) Calculated for $C_{20}H_{20}N_2NaO_2$: 343.1417. Found $[M + Na]^+$: 343.1408.

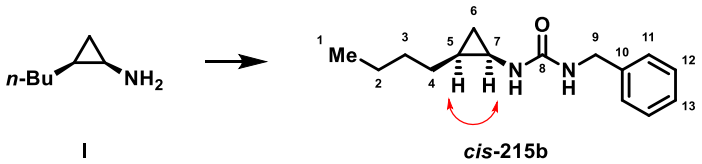
1,3-Dibenzyl-5-butyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (207b) *and* 1,3- Dibenzyl-6-butyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (208b)



General Procedure B: *Urea **cis-206b** was synthesised by McCreanor*[103]: Urea ***cis*-206b** (50.5 mg, 0.150 mmol) and $[Rh(cod)_2]OTf$ (7.5 mol%) were employed, and the reaction was stirred for 73 h at 100 °C. The crude mixture was purified by FCC (50% EtOAc/hexane) to yield the title compound **207b** (34.6 mg, 64%) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 6:1

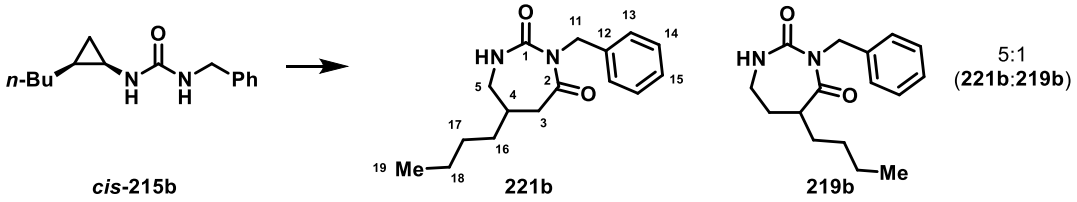
(**207b**:**208b**) mixture of products. **Data for major compound 207b:** ν_{max} / cm^{-1}: 1697 (m), 1647 (s), 1412 (m), 1215 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.24 (8H, m, 2 × C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 7.08–7.06 (2H, m, 2 × C**8**-H), 5.75 (1H, t, *J* = 1.0 Hz, C**5**-H), 5.05 (2H, s, C**11**-H_2), 4.72 (2H, s, C**6**-H_2), 3.04 (2H, s, C**3**-H_2), 2.14 (2H, td, *J* = 7.0, 1.0 Hz, C**16**-H_2), 1.45–1.39 (2H, m, C**17**-H_2), 1.27–1.18 (2H, m, C**18**-H_2), 0.87 (3H, t, *J* = 7.5 Hz, C**19**-H_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.7 (C**2**), 154.1 (C**1**), 137.7 (C**12**), 136.3 (C**7**), 128.7, 128.3, 128.1, 128.0, 127.7, 127.6, 127.2 (C**4**, C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 124.1 (C**5**), 53.0 (C**6**), 47.5 (C**11**), 39.4 (C**3**), 33.7 (C**16**), 29.0 (C**17**), 21.9 (C**18**), 13.7 (C**19**); HRMS: (ESI^+) Calculated for $C_{23}H_{27}N_2O_2$: 363.2067. Found $[M + H]^+$: 363.2078.

(1*R,2*S**)-1-Benzyl-3-(2-butylcyclopropyl)urea (*cis*-215b)**



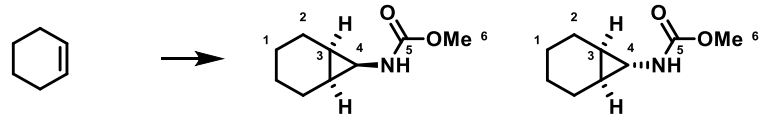
General procedure A: *cis-Cyclopropylamine **I** was synthesised by McCreanor*[103]: Amine **I** (283 mg, 2.50 mmol) and benzyl isocyanate (309 μL, 2.50 mmol) were employed. The crude mixture was purified by FCC (75% EtOAc/hexane) to yield the title compound (430 mg, 70%) as a colourless solid; m.p. 66–68 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3319 (s), 2927 (s), 1625 (s), 1572 (s), 1267 (s), 1240 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31–7.22 (5H, m, 2 × C**11**-H, 2 × C**12**-H, C**13**-H), 5.44 (1H, br. s, NH), 4.92 (1H, br. s, NH), 4.40 (2H, d, *J* = 6.0 Hz, C**9**-H_2), 2.45 (1H, m, C**7**-H), 1.45 (1H, m, 1 × C**4**-H), 1.37–1.28 (4H, m, C**2**-H_2, C**3**-H_2), 1.19 (1H, m, 1 × C**4**-H), 0.89–0.84 (4H, m, C**1**-H_3, 1 × C**6**-H), 0.13 (1H, m, 1 × C**6**-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.5 (C**8**), 139.5 (C**10**), 128.5, 127.4, 127.2 (C**11**, C**12**, C**13**), 44.2 (C**9**), 31.7 (C**3**), 27.0 (C**4**), 26.7 (C**7**), 22.6 (C**2**), 18.1 (C**5**), 14.0 (C**1**), 12.8 (C**6**); HRMS: (ESI+) Calculated for $C_{15}H_{23}N_2O$: 247.1805. Found $[M + H]^+$: 247.1804. *The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C7-H to C5-H. No significant nOe was observed between C7-H and C4-H_2.*

3-Benzyl-6-butyl-1,3-diazepane-2,4-dione (221b) *and* 3-Benzyl-5-butyl-1,3-diazepane-2,4-dione (219b)



General Procedure B: Urea ***cis*-215b** (37.0 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (7.5 mol%) were employed, and the reaction was stirred for 38 h at 90 °C. The crude mixture was purified by FCC (20% EtOAc/hexane) to yield the title compound **221b** and **219b** (24.0 mg, 58%, 10:1, **221b**:**219b**) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 5:1 (**221b**:**219b**) mixture of products. **Data for product 221b:** ν_{max} / cm^{-1}: 3304 (m), 2925 (m), 1709 (s), 1537 (s), 1260 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.75 (1H, br. s, N<u>H</u>), 7.39–7.20 (5H, m, 2 × C**8**-<u>H</u>, 2 × C**9**-<u>H</u>, C**10**-<u>H</u>), 4.50 (2H, d, *J* = 6.0 Hz, C**6**-<u>H$_2$</u>), 4.04 (1H, dd, *J* = 11.0, 7.5 Hz, 1 × C**5**-<u>H</u>), 3.44 (1H, dd, *J* = 11.0, 7.0 Hz, 1 × C**5**-<u>H</u>), 2.69 (1H, m, 1 × C**3**-<u>H</u>), 2.35–2.26 (2H, m, 1 × C**3**-<u>H</u>, C**4**-<u>H</u>), 1.52–1.26 (6H, m, C**11**-<u>H$_2$</u>, C**12**-<u>H$_2$</u>, C**13**-<u>H$_2$</u>), 0.91 (3H, t, *J* = 7.0 Hz, C**14**-<u>H$_3$</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.7 (C**2**), 153.0 (C**1**), 138.3 (C**7**), 128.6, 127.6, 127.3 (C**8**, C**9**, C**10**), 51.2 (C**5**), 43.8 (C**6**), 39.9 (C**3**), 33.8 (C**11**), 30.7 (C**4**), 29.5 (C**12**), 22.6 (C**13**), 13.9 (C**14**); HRMS: (ESI$^+$) Calculated for $C_{16}H_{22}N_2NaO_2$: 297.1573. Found [M + Na]$^+$: 297.1572. **Data for product 219b:** *Partial characterisation on S37.*

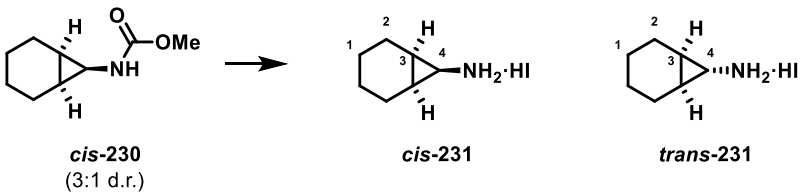
Methyl ((1*R,6*S**,7*S**)-bicyclo[4.1.0]heptan-7-yl)carbamate (*cis*-230) *and* Methyl ((1*R**,6*S**,7*R**)-bicyclo[4.1.0]heptan-7-yl) (*tran*-230)**



Adapted from a literature procedure[155]: Methyl carbamate (2.40 g, 32.0 mmol), copper powder (889 mg, 14.0 mmol), zinc powder (13.1 g, 200 mmol) and $ZnCl_2$ (4.22 g, 31.0 mmol) were suspended in dry Et_2O (50 mL) in a flame-dried flask under an atmosphere of nitrogen. Cyclohexene (1.01 mL, 10.0 mmol) was added followed by the dropwise addition of freshly distilled (Hickman still) TMSCl (14.0 mL, 110 mmol) over 30 minutes at room temperature. Triethyl orthoformate (6.15 mL, 37.0 mmol) was then added by syringe pump (1.1 mL/hr). The reaction mixture was stirred for 18 h at room temperature before the addition of sat. aq. $NaHCO_3$ (150 mL). The resulting biphasic solution was filtered through a short pad of celite, separated and the aqueous solution was further extracted with Et_2O (3 × 50 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was dissolved in MeOH (10 mL), and K_2CO_3 (2 g) was added before stirring for 1 hr. The reaction mixture was concentrated *in vacuo*, dissolved in water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were washed with brine (150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by FCC (10% EtOAc/Hexane) to yield the title compounds (1.53 g, 90%, 3:1 d.r.) as a pale yellow oil. *The product diastereomers were inseparable by FCC.* **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 3317 (br.), 2930 (m), 1702 (s), 1519 (m), 1449 (m), 1240 (m), 1076 (m); **Data for major diasteromer *cis*-230:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.57 (1H, br. s, N<u>H</u>), 3.77–3.61 (3H, br. s, C**6**-<u>H$_3$</u>), 2.52 (1H, br. m, C**4**-<u>H</u>), 1.95–1.82 (2H, m, 2 × C**1**/**2**-<u>H$_2$</u>), 1.39–1.00 (8H, m, 6 × C**1**/**2**-<u>H$_2$</u>, 2 × C**3**-<u>H</u>); **Data for minor compound *trans*-230:** ^{1}H NMR (400 MHz,

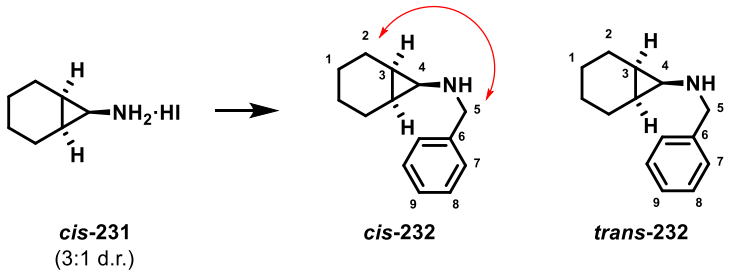
$CDCl_3$): δ 4.80 (1H, br. s, NH), 3.77–3.61 (3H, br. s, C**6**-H_3), 2.24 (1H, br. m, C**4**-H), 1.75–1.66 (2H, m, 2 × C**1**/**2**-H_2), 1.39–1.00 (6H, m, 4 × C**1**/**2**-H_2, 2 × C**3**-H). *The spectroscopic properties of this compound were consistent with that available in the literature*.[155]

(1*R,6*S**,7*S**)-Bicyclo[4.1.0]heptan-7-amine hydroiodide (*cis*-231) *and* (1*R**,6*S**,7*R**)-Bicyclo[4.1.0]heptan-7-amine hydroiodide (*trans*-231)**



Iodotrimethylsilane (2.45 mL, 17.2 mmol) was added To a stirring solution of carbamate ***cis*-230** (1.46 g, 8.61 mmol, 3:1 d.r.) in CH_2Cl_2 (86 mL) at room temperature. The reaction mixture was heated at reflux for 1 h before cooling to room temperature. MeOH (17 mL) was added and the reaction mixture was heated at reflux for 30 minutes before being cooled to room temperature and concentrated *in vacuo*. The resulting orange solid was suspended in Et_2O (20 mL) and filtered, washing with Et_2O, to yield the title compounds (1.79 g, 87%, 3:1 d.r.,) as a brown solid. *The product diastereomers were not separable at this point.* **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 2922 (s), 1571 (m), 1352 (m), 1066 (s); HRMS: (ESI^+) Calculated for $C_7H_{14}N$: 112.1121. Found $[M+H]^+$: 112.1123. **Data for major compound *cis*-231:** ^1H NMR (MeOD-d_4, 400 MHz): δ 2.53 (1H, t, *J* = 8.0 Hz, C**4**-H), 2.13–2.03 (2H, m, 2 × C**2**-H_2), 1.56–1.46 (2H, m, 2 × C**2**-H_2), 1.46–1.36 (2H, m, 2 × C**1**-H_2), 1.33–1.13 (4H, m, 2 × C**1**-H_2, 2 × C**3**-H); ^{13}C NMR (MeOD-d_4, 100 MHz): δ 31.1 (C**4**), 22.0 (C**1**), 17.7 (C**2**), 11.4 (C**3**). **Data for minor compound *trans*-231:** ^1H NMR (MeOD-d_4, 400 MHz): δ 2.36 (1H, t, *J* = 8.0 Hz, C**4**-H), 1.98–1.85 (2H, m, 2 × C**2**-H_2), 1.76–1.67 (2H, m, 2 × C**2**-H_2), 1.35–1.07 (6H, m, 4 × C**1**-H_2, 2 × C**3**-H); ^{13}C NMR (MeOD-d_4, 100 MHz): δ 34.1 (C**4**), 22.4 (C**2**), 21.8 (C**1**), 17.0 (C**3**).

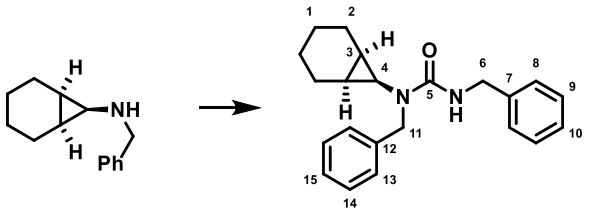
(1*R,6*S**,7*S**)-*N*-Benzylbicyclo[4.1.0]heptan-7-amine (*cis*-232) *and* (1*R**,6*S**,7*R**)-*N*-Benzylbicyclo[4.1.0]heptan-7-amine (*trans*-232)**



To a stirring solution of amine·hydroiodide salt ***cis*-231** (1.50 g, 6.30 mmol, 3:1 d.r.) in MeOH (14 mL) was added $NaHCO_3$ (2.11 g, 25.1 mmol) and benzaldehyde (0.58 mL, 5.65 mmol), and the reaction mixture was heated at reflux for 8 h. The reaction mixture was cooled to 0 °C before $NaBH_4$ (285 mg,

7.52 mmol) was added portion-wise. The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated *in vacuo* before adding water (80 mL) and extracting with CH_2Cl_2 (3 × 30 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FCC (30% EtOAc/hexane) to afford ***cis*-232** (807 mg, 71%) as a pale yellow oil and ***trans*-232** (267 mg, 23%) as a pale yellow oil. **Data for product *cis*-232:** ν_{max} / cm^{-1}: 3290 (br.), 2927 (s), 1642 (s), 1542 (m), 1495 (m), 1452 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.21 (5H, m, 2 × C**7**-H, 2 × C**8**-H, C**9**-H), 3.81 (2H, s, C**5**-H_2), 2.03 (1H, t, *J* = 7.5 Hz, C**4**-H), 1.85–1.73 (2H, m, 2 × C**2**-H), 1.59–1.49 (2H, m, 2 × C**2**-H), 1.47–1.31 (2H, m, 2 × C**1**-H), 1.30–1.17 (2H, m, 2 × C**1**-H), 0.86–0.83 (2H, m, 2 × C**3**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.4 (C**6**), 128.4, 128.3, 126.9 (C**7**, C**8**, C**9**), 54.0 (C**5**), 36.4 (C**4**), 22.8 (C**1**), 18.5 (C**2**), 12.3 (C**3**); HRMS: (ESI^+) Calculated for $C_{14}H_{20}N$: 202.1590. Found $[M+H]^+$: 202.1596. *The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). An nOe was observed between C**5**-H_2 and C**2**-H_2. No significant nOe was observed between C**5**-H_2 and C**3**-H.* **Data for product *trans*-232:** ν_{max} / cm^{-1}: 2923 (s), 2850 (s), 1449 (s), 1295 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.23 (5H, m, 2 × C**7**-H, 2 × C**8**-H, C**9**-H), 3.81 (2H, s, C**5**-H_2), 1.89–1.80 (3H, m, 2 × C**2**-H, C**4**-H), 1.72 (1H, br. s, NH), 1.62–1.55 (2H, m, 2 × C**2**-H), 1.25–1.16 (2H, m, 2 × C**1**-H), 1.09–1.01 (2H, m, 2 × C**2**-H), 0.94–0.87 (2H, m, 2 × C**3**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.7 (C**6**), 128.3, 128.3, 126.8 (C**7**, C**8**, C**9**), 53.6 (C**5**), 42.3 (C**4**), 23.0 (C**2**), 21.8 (C**1**), 18.8 (C**3**); HRMS: (ESI^+) Calculated for $C_{14}H_{20}N$: 202.1590. Found $[M + H]^+$: 202.1589.

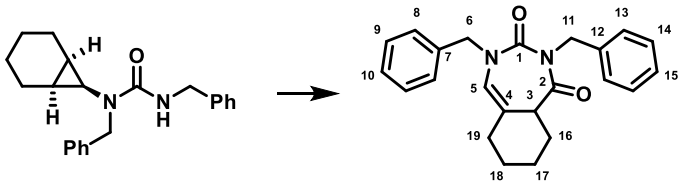
1,3-Dibenzyl-1-((1*R,6*S**,7*S**)-bicyclo[4.1.0]heptan-7-yl)urea (*cis*-222)**



***cis*-232** ***cis*-222**

General procedure A: Amine ***cis*-232** (750 mg, 3.73 mmol) was employed and the residue was purified by FCC (15–20% EtOAc/hexane) to provide the title compound (1.16 g, 93%) as a colourless solid; m.p. 105–107 °C ($CHCl_3$/hexane); ν_{max} / cm^{-1}: 2924 (w), 1632 (s), 1504 (s), 1278 (m), 1231 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, 70 °C): δ 7.32–7.19 (10H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, 2 × C**15**-H), 6.63 (1H, m, NH), 4.53 (2H, br. s, C**11**-H_2), 4.33 (2H, d, *J* = 5.9 Hz, C**6**-H_2), 2.23 (1H, t, *J* = 7.4 Hz, C**4**-H), 1.82 (2H, m, 2 × C**2**-H), 1.56 (2H, m, 2 × C**2**-H), 1.30–1.17 (4H, m, C**1**-H), 1.10 (2H, m, C**3**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2 (C**5**), 140.2 (C**7**), 138.5 (C**12**), 127.6, 127.5, 127.3, 126.8, 126.2, 125.9 (C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 49.8 (C**11**), 43.5 (C**6**), 34.1 (C**4**), 20.7 (C**1**), 18.5 (C**2**), 13.9 (C**3**); HRMS: (ESI^+) Calculated for $C_{22}H_{26}N_2NaO$: 357.1937. Found $[M + Na]^+$: 357.1937.

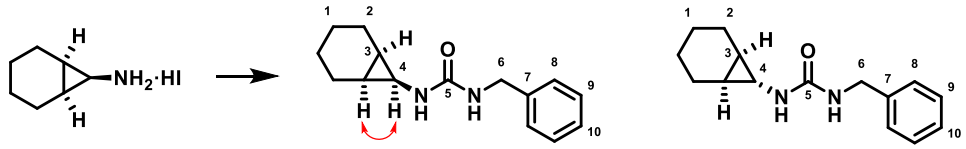
2,4-Dibenzyl-4,6,7,8,9,9a-hexahydro-1*H*-benzo[e][1,3]diazepine-1,3(2*H*)-dione (227)



***cis*-222** **227**

General Procedure B: Urea ***cis*-222** (50.2 mg, 0.150 mmol) and $[Rh(cod)_2]BARF$ (10.0 mol%) were employed, and the reaction was stirred for 96 h at 90 °C. The crude mixture was purified by FCC (10% EtOAc/hexane) to yield the title compound (28.2 mg, 54%) as a colourless oil; ν_{max} / cm^{-1}: 2934 (w), 2863 (w), 1697 (s), 1645 (s), 1404 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.24 (8H, m, 2 × C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 7.07–7.05 (2H, m, C**8**-H), 5.82 (1H, s, C**5**-H), 5.24 (1H, d, *J* = 14.5 Hz, C**11**-H), 4.92–4.84 (2H, m, 1 × C**6**-H, 1 × C**11**-H), 4.59 (1H, d, *J* = 15.0 Hz, C**6**-H), 3.16 (1H, m, C**3**-H), 2.39 (1H, m, C**16**-H), 2.27 (1H, m, C**18**-H), 2.13 (1H, m, C**16**-H), 1.81–1.67 (3H, m, 1 × C**17**-H, C**18**-H, C**19**-H), 1.50 (1H, m, C**19**-H), 1.33 (1H, m, C**17**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7 (C**2**), 154.5 (C**1**), 138.0 (C**12**), 136.4 (C**7**), 128.8, 128.5, 128.4, 128.2, 127.7, 127.2 (C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 123.2 (C**5**), 52.8 (C**6**), 47.7 (C**11**), 41.2 (C**3**), 27.0 (C**16**), 23.1 (C**17**), 22.7 (C**19**), 22.1 (C**18**); HRMS: (ESI^+) Calculated for $C_{23}H_{24}N_2NaO_2$: 383.1730. Found $[M + Na]^+$: 383.1739.

1-Benzyl-3-((1*R,6*S**,7*S**)-bicyclo[4.1.0]heptan-7-yl)urea (*cis*-233) *and* 1-Benzyl-3-((1*R**,6*S**,7*S**)-bicyclo[4.1.0]heptan-7-yl)urea (*trans*-233)**

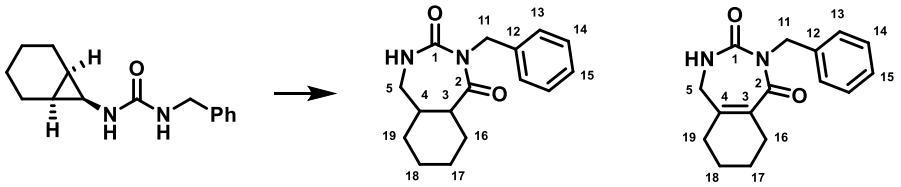


***cis*-232** (3:1 d.r.) ***cis*-233** ***trans*-233**

General procedure A: Amine·hydroiodide salt ***cis*-232** (480 mg, 3.73 mmol, 3:1 d.r.) was employed and the residue was purified by FCC (50% EtOAc/hexane) to provide the title compound (378 mg, 77%, 4:1 d.r.,) as a colourless oil. **Data for the mixture of diastereomers:** ν_{max} / cm^{-1}: 3316 (s), 2924 (s), 2850 (s), 1629 (s), 1565 (s), 1249 (s); *m/z* (ESI^+) HRMS: Calculated for $C_{15}H_{21}N_2O$: 245.1648. Found $[M + H]^+$: 245.1646. **Data for major diastereomer *cis*-233:** ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.25 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 5.23 (1H, br. s, NH), 4.47 (2H, d, *J* = 6.0 Hz, C**6**-H_2) 2.33 (1H, t, *J* = 7.0 Hz, C**4**-H), 1.87 (2H, m, 2 × C**2**-H), 1.44–1.34 (2H, m, 2 × C**2**-H), 1.27–1.18 (4H, m, 4 × C**1**-H), 1.08–1.03 (2H, m, 2 × C**3**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3 (C**5**), 139.5 (C**7**), 128.7, 127.6, 127.3 (C**8**, C**9**, C**10**), 44.4 (C**6**), 29.0 (C**4**), 21.8 (C**1**), 18.0 (C**2**), 12.2 (C**3**). *The relative stereochemistry of this compound was corroborated by nOe experiments (as indicated on the compound structure). A strong nOe was observed between C4-H to C3-H.* **Data for minor diastereomer**

***trans*-233:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.05 (1H, br. s, NH), 4.66 (1H, br. s, NH), 2.11 (1H, m, C**4**-H), 1.66–1.58 (2H, m, 2 × C**2**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3 (C**5**), 139.6 (C**7**), 128.7, 127.2, (ArCH), 44.1 (C**6**), 34.0 (C**4**), 22.3 (C**2**), 21.3 (C**1**), 19.7 (C**3**).

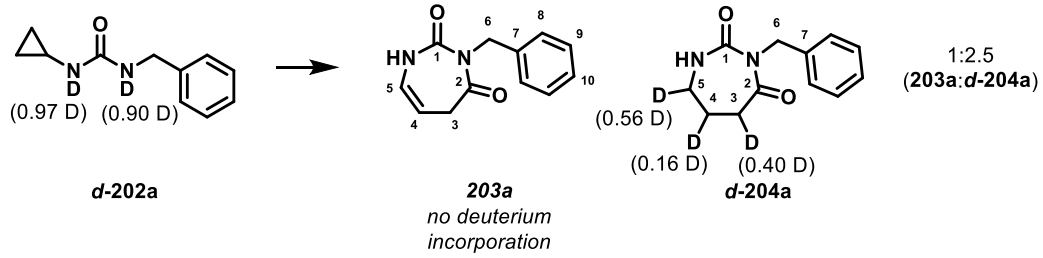
(5a*S,9a*R**)-2-Benzyloctahydro-1*H*-benzo[e][1,3]diazepine-1,3(2*H*)-dione (235) *and* 2-Benzyl-4,5,6,7,8,9-hexahydro-1*H*-benzo[e][1,3]diazepine-1,3(2*H*)-dione (234)**



cis-233 235 234

General Procedure B: Urea ***cis*-233** (36.7 mg, 0.150 mmol, 4:1 d.r.) and $[Rh(cod)_2]BARF$ (7.5 mol%) were employed, and the reaction was stirred for 48 h at 110 °C. The crude mixture was purified by FCC (15–25% EtOAc/hexane) to yield title compound **235** (20.7 mg, 51%) as a pale brown oil and **234** (6.80 mg, 17%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 3:1 (**234**:**235**) mixture of products. **Data for major product 235:** ν_{max} / cm^{-1}: 3304 (m), 2929 (m), 1707 (s), 1536 (s), 1380 (s), 1247 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.76 (1H, br. s, NH), 7.35–7.24 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 4.53 (1H, ddd, *J* = 15.0, 5.5 Hz, 1 × C**6**-H), 4.47 (1H, dd, *J* = 15.0, 5.5 Hz, 1 × C**6**-H), 3.67 (1H, dd, *J* = 11.0, 6.0 Hz, 1 × C**5**-H), 3.61 (1H, dd, *J* = 11.0, 2.0 Hz, 1 × C**5**-H), 2.69 (1H, td, *J* = 7.0, 4.0 Hz, C**3**-H), 2.33 (1H, m, C**4**-H), 2.04 (1H, m, 1 × C**14**-H), 1.76 (1H, m, 1 × C**11**-H), 1.64–1.50 (3H, m, 1 × C**12**-H, 1 × C**13**-H, 1 × C**14**-H), 1.27–1.13 (3H, m, 1 × C**11**-H, 1 × C**12**-H, 1 × C**13**-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 178.1 (C**2**), 153.5 (C**1**), 138.2 (C**7**), 128.6, 127.6, 127.3 (C**8**, C**9**, C**10**), 49.3 (C**5**), 44.2 (C**3**), 43.8 (C**6**), 31.2 (C**4**), 27.7 (C**11**), 23.4 (C**12**), 22.9 (C**14**), 22.6 (C**13**); HRMS: (ESI^+) Calculated for $C_{16}H_{20}N_2NaO_2$: 295.1417. Found $[M + Na]^+$: 295.1424. **Data for minor product 234:** ν_{max} / cm^{-1}: 3298 (m), 2930 (m), 1699 (s), 1679 (m), 1537 (s), 1356 (s), 1250 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.75 (1H, br. s, NH), 7.35–7.22 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 4.53 (2H, d, *J* = 6.0 Hz, C**6**-H_2), 4.26 (2H, s, C**5**-H_2), 2.35–2.32 (2H, m, C**14**-H_2), 2.21–2.17 (2H, m, C**11**-H_2), 1.79–1.70 (4H, m, C**12**-H_3, C**13**-H_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2 (C**2**), 154.8 (C**4**), 152.7 (C**1**), 138.5 (C**7**), 131.3 (C**3**), 128.6, 127.5, 127.2 (C**8**, C**9**, C**10**), 51.5 (C**5**), 43.6 (C**6**), 24.4 (C**14**), 21.7, 21.5 (C**12**, C**13**), 19.8 (C**11**); HRMS: (ESI^+) Calculated for $C_{16}H_{18}N_2NaO_2$: 293.1260. Found $[M + Na]^+$: 293.1264.

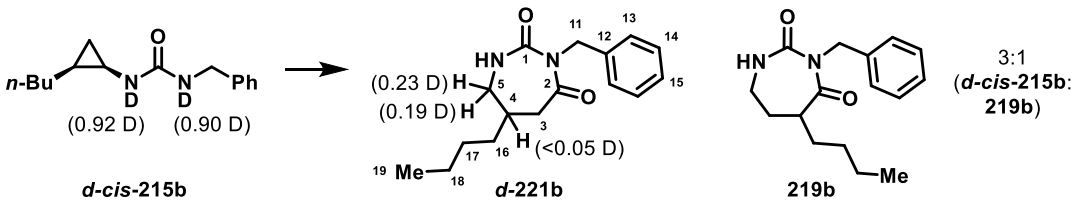
3-Benzyl-1,3-diazepane-2,4-dione (*d*-204a) *and* 1-Benzyl-3,6-dihydro-1*H*-1,3-diazepine-2,7-dione (203a)



***d*-202a** was initially prepared by repeatedly dissolving **202a** in MeOD-d_4 and concentrating the resulting solution *in-vacuo*. *97% deuterium incorporation at N**1** and 90% deuterium incorporation at N**2** was measured by ^{1}H NMR.* **Data for *d*-202a:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.25 (2 × C**6**-H, 2 × C**7**-H, C**8**-H), 5.31 (0.03H, br. s, NH), 4.79 (0.10H, br. s, NH), 4.47 (2H, d, *J* = 6.0 Hz, C**4**-H_2), 2.46 (1H, tt, *J* = 7.0, 3.5 Hz, C**2**-H), 0.76-0.71 (2H, m, 2 × C**1**-H), 0.60-0.57 (2H, m, 2 × C**1**-H). *$CDCl_3$ was base filtered (K_2CO_3 plug) prior to use.*

General Procedure B: Urea ***d*-202a** (28.5 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (5.0 mol%) were employed, and the reaction was stirred for 24 h at 90 °C. The crude mixture was purified by FCC (30% EtOAc/hexane) to yield the title compound (20.5 mg**,** 63%, 2.5:1, ***d*-204a**:**203a**) as a yellow oil. *Analysis of the product revealed 56% deuterium incorporation at C**5**, 16% at C**4** and 40% at C**3**. No deuterium incorporation was observed in **8l**.* **Data for product *d*-204a:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.79 (1H, br. s, NH), 7.35–7.21 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 4.50 (2H, d, *J* = 6.0 Hz, C**6**-H_2), 3.89 (1.44H, t, *J* = 7.0 Hz, C**5**-H_2), 2.61 (1.60H, t, *J* = 7.0 Hz, C**3**-H_2), 2.04 (1.84H, tt, *J* = 7.0, 7.0 Hz, C**4**-H_2); ^{2}H NMR ($CHCl_3$, 500 MHz): δ 3.89 (0.56D, br. s, C**5**-D), 2.60 (0.49D, br. s, C**3**-D), 2.02 (0.06D, br. s, C**4**-D).

3-Benzyl-6-butyl-1,3-diazepane-2,4-dione (*d*-221b) *and* 3-Benzyl-5-butyl-1,3-diazepane-2,4-dione (219b)

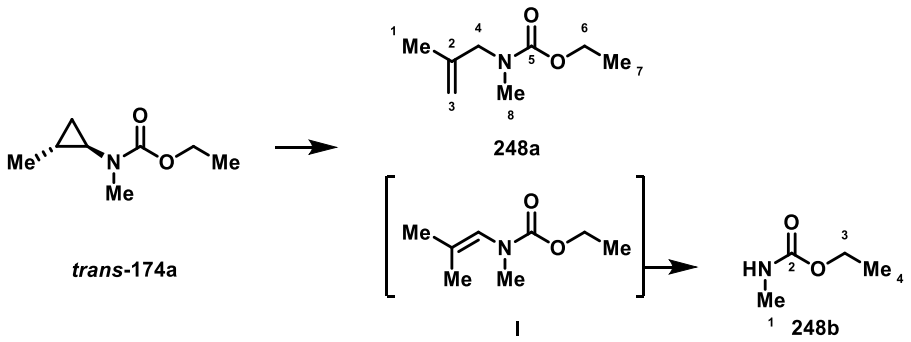


***d*-*cis*-215b** was initially prepared by repeatedly dissolving ***cis*-215b** in MeOD-d_4 and concentrating the resulting solution *in-vacuo*. *92% deuterium incorporation at N**1** and 90% deuterium incorporation at N**2** was measured by ^{1}H NMR.* **Data for *d*-*cis*-215b:** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31–7.22 (5H, m, 2 × C**11**-H, 2 × C**12**-H, C**13**-H), 5.44 (0.08H, br. s, NH), 4.92 (0.10H, br. s, NH), 4.40 (2H, d, *J* = 6.0 Hz, C**9**-H_2), 2.45 (1H, m, C**7**-H), 1.45 (1H, m, 1 × C**4**-H), 1.37–1.28 (4H, m, C**2**-H_2, C**3**-H_2), 1.19

(1H, m, 1 × C**4**-H), 0.89–0.84 (4H, m, C**1**-H_3, 1 × C**6**-H), 0.13 (1H, m, 1 × C**6**-H). *$CDCl_3$ was base filtered (K_2CO_3 plug) prior to use.*

General Procedure B: Urea ***d-cis*-215b** (37.0 mg, 0.150 mmol) and [Rh(cod)$_2$]BARF (7.5 mol%) were employed, and the reaction was stirred for 43 h at 90 °C. The crude mixture was purified by FCC (20% EtOAc/hexane) to yield the title compound ***d*-221b** (19.2 mg**,** 47%) as a yellow oil. *Analysis of the product revealed 23% and 19% deuterium incorporation at the diastereotopic C**5** positions. <5% deuterium incorporation was measured at C**4**. **219b** could not be isolated in a pure form and therefor deuterium incorporation could not be confirmed.* **Data for product *d*-221b:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.75 (1H, br. s, NH), 7.39–7.20 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 4.50 (2H, d, *J* = 6.0 Hz, C**6**-H_2), 4.04 (0.81H, dd, *J* = 11.0, 7.5 Hz, 1 × C**5**-H), 3.44 (0.77H, dd, *J* = 11.0, 7.0 Hz, 1 × C**5**-H), 2.69 (1H, m, 1 × C**3**-H), 2.35–2.26 (1.96H, m, 1 × C**3**-H, C**4**-H), 1.52–1.26 (6H, m, C**11**-H_2, C**12**-H_2, C**13**-H_2), 0.91 (3H, t, *J* = 7.0 Hz, C**14**-H_3). ^{2}H NMR ($CHCl_3$, 500 MHz): δ 8.74 (0.34 D, br. s, ND), 4.05 (0.71D, br. s, 1 × C**5**-D), 3.44 (1D, br. s, 1 × C**5**-D), 2.28 (0.04D, br. m, C**4**-D).

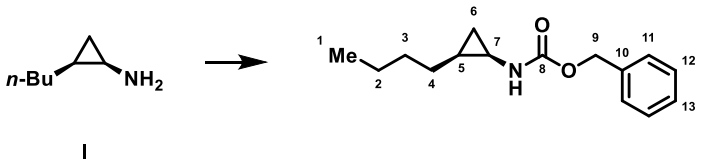
Ethyl methyl(2-methylprop-1-en-1-yl)carbamate (248a) *and* Ethyl methylcarbamate (248b)



*Carbamate **trans-174a** was synthesised by McCreanor[103]*: An oven dried reaction tube, fitted with a magnetic stirrer, was charged with [Rh(cod)$_2$]BF_4 (3.10 mg, 0.00750 mmol) and PPh_3 (5.90 mg, 0.0225 mmol). The tube was fitted with a rubber septum and purged with argon. Carbamate ***trans*-174a** (23.6 mg, 0.150 mmol, single diastereomer) in argon sparged anhydrous toluene (0.75 mL) was added *via* syringe before aging the catalyst for *ca.* 5 minutes. The reaction was heated at 100 °C with stirring for 6 h. The mixture was cooled to room temperature, concentrated *in vacuo* and purified by FCC (5% EtOAc/hexane) to yield the title compounds (15.1 mg, 64%, 10:1, **248a**:**248b**) as a colourless oil. *The presence of **248b** is attributed to hydrolysis of enamine **I** under the reaction conditions. None of the linear* β*-hydride elimination products resulting from insertion into bond b were observed by NMR of the crude reaction mixture.* **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 2978 (w), 1698 (s), 1447 (m), 1382 (m), 1147 (s); HRMS: (ESI$^+$) Calculated for $C_8H_{15}NNaO_2$: 180.1000. Found [M + Na]$^+$: 180.0988. **Data for major compound 248a:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.86 (1H, br. s, C**2**-H), 4.77 (1H, br. s, C**2**-H), 4.14 (2H, q, *J* = 7.0 Hz, C**6**-H_2), 3.80 (2H, m, C**4**-H_2), 2.82 (3H, m, C**8**-H_3), 1.67 (3H, s, C**1**-H_3), 1.26 (3H, m, C**7**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 111.9 (C**2**), 61.4 (C**6**), 54.7 (C**4**),

33.3 (C**8**), 19.9 (C**1**), 14.9 (C**7**). **Data for minor compound 248b:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.98 (3H, s, C**1**-$\underline{H}_3$). *Proton signals corresponding to C**3** and C**4** closely overlap C**6** and C**7** of compound **248b**.*

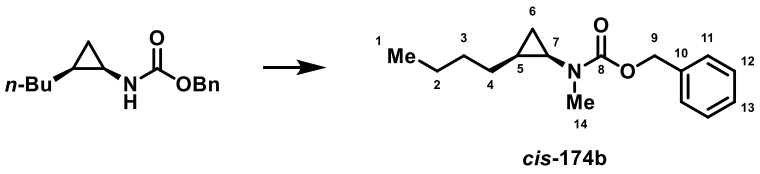
Benzyl ((1*R,2*S**)-2-butylcyclopropyl)carbamate**



I

*Amine **I** was synthesised by McCreanor[103]*: To a stirring solution of amine (100 mg, 0.880 mmol) and NEt_3 (0.150 mL, 1.06 mmol) in CH_2Cl_2 (4.4 mL) was added benzyl chloroformate (150 μL, 1.06 mmol) dropwise at 0 °C over 10 minutes under an atmosphere of nitrogen. The reaction mixture was warmed to room temperature and stirred for 16 h. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by FCC (20% EtOAc/hexane) to yield the title compound (145 mg, 67%) as a colourless oil; ν_{max} / cm^{-1}: 3324 (m), 1700 (s), 1525 (s), 1453 (m), 1259 (s), 1075 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.27 (5H, m, 2 × C**11**-$\underline{H}$, 2 × C**12**-$\underline{H}$, C**13**-$\underline{H}$), 5.16–5.09 (2H, m, C**9**-$\underline{H}_2$), 4.73 (1H, m, N$\underline{H}$), 2.69 (1H, m, C**7**-$\underline{H}$), 1.49–1.18 (6H, m, C**2**-$\underline{H}_2$, C**3**-$\underline{H}_2$, C**4**-$\underline{H}_2$), 0.98–0.83 (5H, m, C**1**-$\underline{H}_3$, C**5**-$\underline{H}$, 1 × C**6**-$\underline{H}$), 0.16 (1H, m, 1 × C**6**-$\underline{H}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.3 (C**8**), 136.7 (C**10**), 128.4, 128.0 (C**11**, C**12**, C**13**), 66.7 (C**9**), 31.7 (C**3**), 27.6 (C**7**), 27.3 (C**4**), 22.5 (C**2**), 17.4 (C**5**), 13.9 (C**1**), 12.3 (C**6**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{22}NO_2$: 248.1645. Found [M + H]$^+$: 248.1642.

Benzyl ((1*R,2*S**)-2-butylcyclopropyl)(methyl)carbamate (*cis*-174b)**

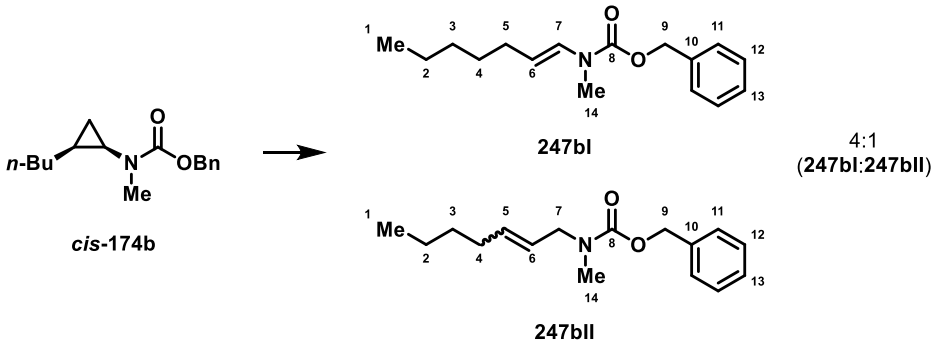


***cis*-174b**

To a solution of NaH (58.0 mg, 2.40 mmol) in THF (1.6 mL) was added a solution of carbamate **I** (120 mg, 0.485 mmol) in THF (0.25 mL) and the reaction was stirred at 0 °C for 1 h. Methyl iodide (150 μL, 2.40 mmol) was added dropwise at 0 °C and the reaction was stirred at room temperature for 18 h. Water (5 mL) was added to the reaction mixture and the solution was extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by FCC (10% EtOAc/hexane) to yield the title compound (99.2 mg, 78%) as a colourless oil; ν_{max} / cm^{-1}: 2927 (s), 1701 (s), 1455 (m), 1391 (s), 1344 (s), 1150 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.28 (5H, m, 2 × C**11**-$\underline{H}$, 2 × C**12**-$\underline{H}$, C**13**-$\underline{H}$), 5.19–5.09 (2H, m, C**9**-$\underline{H}_2$), 2.91 (3H, s, C**14**-$\underline{H}_3$), 2.68 (1H, ddd, *J* = 7.5, 7.0, 4.5 Hz, C**7**-$\underline{H}$), 1.58 (1H, m, 1 × C**4**-$\underline{H}$),

1.37–1.25 (4H, m, C**2**-H$_2$, C**3**-H$_2$), 0.99–0.81 (6H, m, C**1**-H$_3$, 1 × C**4**-H, C**5**-H, 1 × C**6**-H), 0.32 (1H, m, 1 × C**6**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.0 (C**8**), 136.9 (C**10**), 128.4, 127.9 (C**11**, C**12**, C**13**), 67.0 (C**9**), 35.8 (C**14**), 35.4 (C**7**), 31.7 (C**3**), 27.6 (C**4**), 22.6 (C**2**), 19.7 (C**5**), 14.1 (C**1**), 11.9 (C**6**); HRMS: (ESI$^+$) Calculated for $C_{16}H_{23}NNaO_2$: 284.1621. Found [M + Na]$^+$: 284.1623.

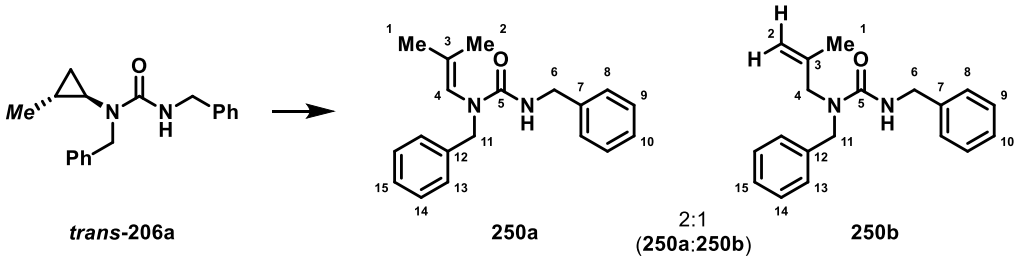
Benzyl (*E*)-hept-1-en-1-yl(methyl)carbamate (247bI) *and* Benzyl hept-2-en-1-yl(methyl)carbamate (247bII)



An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]BF_4$ (3.70 mg, 9.00 μmol) and PPh_3 (7.10 mg, 0.0270 mmol). The tube was fitted with a rubber septum and purged with argon. Carbamate ***cis*-174b** (47.0 mg, 0.180 mmol) in argon sparged anhydrous toluene (2 mL) was added *via* syringe before aging the catalyst for *ca.* 5 minutes. The reaction was heated at 100 °C with stirring for 3 h. The mixture was cooled to room temperature, concentrated *in vacuo* and purified by FCC (5% EtOAc/hexane) to yield regioisomer **247bI** (31.1 mg, 66%, 1:1, mixture of rotamers *A:B*) as a colourless oil and regioisomer **247bII** (9.40 mg, 20%, tentatively assigned mixture of *E*/*Z* diastereomers) as a colourless oil. **Data for the major regioisomer 247bI:** ν_{max} / cm^{-1}: 2928 (m), 1693 (s), 1403 (m), 1214 (m), 1153 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.30 (5H, m, 2 × C**11**-H, *A*+*B*, 2 × C**12**-H, *A*+*B*, C**13**-H, *A*+*B*), 7.01 (0.50H, d, *J* = 14.0 Hz, C**7**-H, *A*), 6.89 (0.50H, d, *J* = 14.0 Hz, C**7**-H, *B*), 5.19 (2H, s, C**9**-H$_2$, *A*+*B*), 4.85 (1H, dt, *J* = 14.0, 7.5 Hz, C**6**-H, *A*+*B*), 3.07–3.05 (3H, m, C**14**-H$_3$, *A*+*B*), 2.08–1.99 (2H, m, C**5**-H$_2$, *A*+*B*), 1.40–1.25 (6H, m, C**2**-H$_2$, *A*+*B*, C**3**-H$_2$, *A*+*B*, C**4**-H$_2$, *A*+*B*), 0.89 (3H, t, J = 7.0 Hz, C**1**-H$_3$, *A*+*B*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.3, 153.9 (C**8**, *A*+*B*), 136.4 (C**10**, *A*+*B*), 128.5, 128.2, 128.0 (C**11**, *A*+*B*, C12, *A*+*B*, C13, *A*+*B*), 127.5 (C**7**, *A*+*B*), 110.0 (C**6**, *A*+*B*), 67.8, 67.6 (C**9**, *A*+*B*), 31.5 (CH$_2$, *A*+*B*), 31.0 (C**14**, *A*+*B*), 30.2 (CH$_2$, *A*+*B*, C**5**, *A*+*B*), 22.5 (CH$_2$, *A*+*B*), 14.1 (C**1**, *A*+*B*). ***C2**, **C3** and **C4** could not be assigned. Aldehyde peaks appear due to decomposition of the product*; HRMS: (ESI$^+$) Calculated for $C_{16}H_{23}NNaO_2$: 284.1621. Found [M + Na]$^+$: 284.1618. **Data for the minor regioisomer 247bII:** ν_{max} / cm^{-1}: 2929 (m), 1705 (s), 1397 (m), 1324 (m), 1256 (s), 1136 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (5H, m, 2 × C**11**-H, 2 × C**12**-H, C**13**-H), 5.55 (1H, m, C**5**-H), 5.39 (1H, m, C**6**-H), 5.13 (2H, s, C**9**-H$_2$), 3.87–3.79 (2H, m, C**7**-H$_2$), 2.88–2.82 (3H, m, C**14**-H$_3$), 2.06–1.97 (2H, m, C**4**-H$_2$), 1.37–1.23 (4H, m, C**2**-H$_2$, C**3**-H$_2$), 0.90 (3H, t, *J* = C**1**-H$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2 (C**8**), 137.0 (C**10**), 133.9 (C**5**), 128.4, 127.8, 127.8 (C**11**,

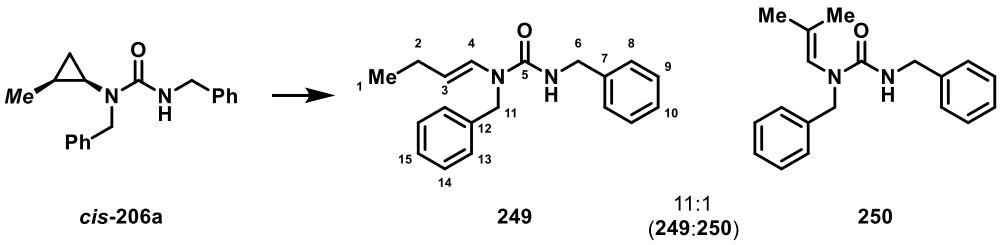
C**12**, C**13**), 124.6 (C**6**), 67.0 (C**9**), 50.6 (C**7**), 33.1 (C**14**), 31.8 (C**4**), 31.3 (CH_2), 22.2 (CH_2), 13.9 (C**1**). *C**2** and C**3** could not be assigned*; HRMS: (ESI$^+$) Calculated for $C_{16}H_{23}NNaO_2$: 284.1621. Found [M + Na]$^+$: 284.1619.

1,3-Dibenzyl-1-(2-methylprop-1-en-1-yl)urea (250a) *and* 1,3-Dibenzyl-1-(2-methylallyl)urea (250b)



*Urea **trans-206a** was synthesised by McCreanor[103]*: Urea ***trans*-206a** (58.9 mg, 0.20 mmol) in anhydrous toluene (2 mL) was added to a resealable tube containing [Rh(cod)$_2$]BF$_4$ (4.00 mg, 0.010 mmol) and PPh$_3$ (7.90 mg, 3.00 μmol) under an atmosphere of argon. The tube was sealed and heated at 100 °C and stirred for 2 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The crude mixture was purified by FCC (25% EtOAc/hexane) to yield title compounds **250a** and **250b** (50.7 mg, 86%, 2:1, r.r.) as a colourless oil. *The isomers could not be separated by FCC*. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 2:1 (**250a**:**250b**) mixture of products. **Data for the mixture of compounds:** ν_{max} / cm^{-1}: 3355 (m), 1643 (s), 1510 (s), 1496 (s), 1434 (m), 1264 (s); HRMS: (ESI$^+$) Calculated for $C_{19}H_{23}N_2O$: 295.1805. Found [M + H]$^+$: 295.1804. **Data for compound 250a:** ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.37–7.23 (10H, m, 2 × C**8**-H, 2 × C**9**- H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 5.67 (1H, s, C**4**-H), 5.11 (1H, t, *J* = 6.0 Hz, NH), 4.62 (2H, s, C**11**-H$_2$), 4.47 (2H, d, *J* = 6.0 Hz, C**6**-H$_2$), 1.66 (3H, s, C**1**/**2**-H$_3$), 1.50 (3H, s, C**1**/**2**-H$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 157.0 (C**5**), 139.8 (C**7**), 138.4 (C**12**), 137.9 (C**3**), 128.6, 128.5. 128.3. 127.5, 127.4, 127.0 (C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 122.3 (C**4**), 51.1 (C**11**), 44.8 (C**6**), 21.9, 17.6 (C**1**, C**2**). **Data for compound 250b:** ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.37–7.23 (10H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 4.92 (1H, s, C**2**-H), 4.89 (1H, s, C**2**-H), 4.86 (1H, br. s, NH), 4.54 (2H, s, C**11**-H$_2$), 4.46 (2H, d, *J* = 6.0 Hz, C**6**-H$_2$), 3.79 (2H, s, C**4**-H$_2$), 1.70 (3H, s, C**1**-H$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 158.5 (C**5**), 141.3 (C**3**), 139.6 (C**7**), 138.0 (C**12**), 128.7, 128.5, 128.4, 127.5, 127.3, 127.1 (C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 111.9 (C**1**), 52.7 (C**4**), 50.4 (C**11**), 44.9 (C**6**), 19.9 (C**1**).

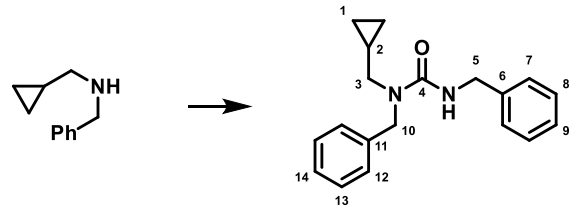
(*E*)-1,3-Dibenzyl-1-(but-1-en-1-yl)urea (249) *and* 1,3-Dibenzyl-1-(2-methylprop-1-en-1-yl)urea (250)



*Urea **cis-206a** was synthesised by McCreanor*[103]: To a resealable tube containing $[Rh(cod)_2]BF_4$ (4.00 mg, 10.0 μmol) and PPh_3 (7.90 mg, 30.0 μmol) under an atmosphere of argon was added urea ***cis*-206a** (58.9 mg, 0.200 mmol) in anhydrous toluene (2 mL). The tube was sealed and heated at 100 °C and stirred for 2 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The crude mixture was purified by FCC (25% EtOAc/hexane) to yield title compound **249** (21.8 mg, 37%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed an 11:1 (**249**:**250**) mixture of products. **Data for compound 249:** ν_{max} / cm^{-1}: 3322 (s), 1628 (s), 1531 (s), 1452 (s), 1248 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.21 (10H, m, 2 × C**8**-H, 2× C**9**-H, C**10**-H, 2 × C**13**-H, 2 × C**14**-H, C**15**-H), 6.81 (1H, d, *J* = 14.0 Hz, C**4**-H), 5.03–4.93 (2H, m, C**3**-H, NH), 4.73 (2H, s, C**11**-H_2), 4.44 (2H, d, *J* = 5.5 Hz, C**6**-H_2), 2.02 (2H, dq, *J* = 7.0, 7.0 Hz, C**2**-H_2), 0.95 (3H, t, *J* = 7.0 Hz, C**1**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0 (C**5**), 139.1 (C**7**), 137.3 (C**12**), 128.7, 128.6, 127.5, 127.3, 127.2, 126.8, 126.5 (C**4**, C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 114.8 (C**3**), 48.7 (C**11**), 44.9 (C**6**), 23.5 (C**2**), 14.7 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{19}H_{23}N_2O$: 295.1805. Found $[M + H]^+$: 295.1808.

4.3 Experimental procedures for the studies in Section 2.2

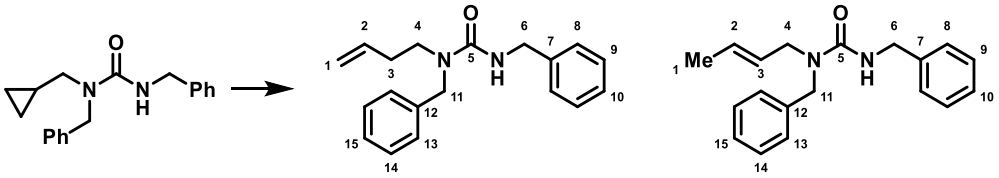
1,3-Dibenzyl-1-(cyclopropylmethyl)urea (263a)



I **263a**

*Amine **I** was synthesised by McCreanor*[359]: To a stirring solution of amine **I** (1.77 g, 11.0 mmol) in CH_2Cl_2 (33 mL), was added benzyl isocyanate (1.24 mL, 10.0 mmol). The reaction mixture was stirred for 2 h before being diluted with CH_2Cl_2 (100 mL) and washed with 1M aq. HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (50% EtOAc/hexane) provided the title compound (2.46 g, 83%) as a colourless solid; m.p. (CH_2Cl_2/ hexane); 86–88 °C; ν_{max} / cm^{-1}: 3305 (s), 1616 (s), 1540 (s), 1454 (s), 1266 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.17 (10H, m, 2 × C**7**-H, 2 × C**8**-H, C**9**-H, 2 × C**12**-H, 2 × C**13**-H, C**14**-H), 4.82 (1H, t, *J* = 5.5 Hz, NH), 4.57 (2H, s, C**10**-H_2), 4.40 (2H, d, *J* = 5.5 Hz, C**5**-H_2), 3.21 (2H, d, *J* = 6.5 Hz, C**3**-H_2), 0.96 (1H, m, C**2**-H), 0.50–0.45 (2H, m, 2 × C**1**-H_2), 0.18–0.14 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.2 (C**4**), 139.6 (C**6**), 138.1 (C**11**), 128.7, 128.5, 127.4, 127.3, 127.1, 126.9 (C**7**, C**8**, C**9**, C**12**, C**13**, C**14**), 51.6 (C**3**), 50.6 (C**10**), 44.9 (C**5**), 10.2 (C**2**), 3.8 (C**1**); HRMS: (ESI^+) Calculated for $C_{19}H_{23}N_2O$: 295.1805. Found $[M + H]^+$: 295.1808.

1,3-Dibenzyl-1-(but-3-en-1-yl)urea (267a) *and* (*E*)-1,3-Dibenzyl-1-(but-2-en-1-yl)urea (267b)

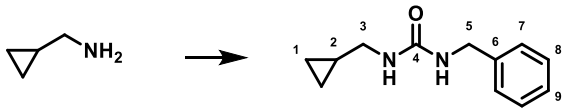


263a **267a** **267a**

General procedure B: [Rh(cod)$_2$]BARF (13.3 mg, 0.0113 mmol), dppe (4.48 mg, 0.0113 mmol) and urea **263a** (44.2 mg, 0.150 mmol) were employed in 1,2-DCB (0.75 mL) at 140 °C for 18 h. Purification by FCC (30% EtOAc/ hexane) provided title compounds **267** (22.0 mg, 50%, 1:2.5 mixture of regioisomers **267a** (A) and **267b** (B)) as a colourless oil; ν_{max} / cm^{-1}: 3342 (br.), 1626 (s), 1529 (s), 1495 (m), 1244 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.14 (20H, m, 4 × C**8**-H, 4 × C**9**-H, 2 × C**10**-H, 4 × C**13**-H, 4 × C**14**-H, 2 × C**15**-H, A+B), 5.79 (1H, ddt, *J* = 17.0, 10.0, 7.0 Hz, C**2**-H, A), 5.58 (1H, m, C**2**-H, B), 5.41 (1H, m, C**3**-H, B), 5.10–5.01 (2H, m, C**1**-H_2, A), 4.78 (1H, NH, A), 4.68 (1H, NH, B), 4.51–4.51 (4H, m, 4 × C**11**-H_2, A+B), 4.44–4.41 (4H, m, 4 × C**6**-H_2, A+B), 3.80 (2H, d, *J* = 6.0 Hz, C**4**-H_2, B), 3.39 (2H, t, *J* = 7.0 Hz, C**4**-H_2, A), 2.33 (2H, m, C**3**-H_2, A), 1.67 (3H, ddt, *J* = 6.5, 1.5,

1.5 Hz, C**1**-H$_3$, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4 (C**5**, A+B), 139.7, 139.7 (C**7**, A+B), 138.3 (C**12**, A+B), 135.4 (C**2**, A), 128.9, 128.9, 128.8, 128.6 (ArC-H, A+B), 128.5 (C**2**, B), 127.6, 127.5, 127.4, 127.2, 127.0 (ArC-H, A+B), 126.8 (C**3**, B), 117.1 (C**1**, A), 50.3 (C**11**, A+B), 49.0 (C**4**, B), 47.4 (C**4**, A), 45.0 (C**6**, A+B), 33.0 (C**3**, A), 17.7 (C**1**, B); HRMS: (ESI$^+$) Calculated for $C_{19}H_{23}N_2O$: 295.1732. Found $[M + H]^+$: 295.1811.

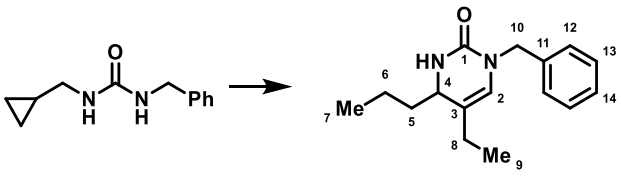
1-Benzyl-3-(cyclopropylmethyl)urea (263b)



263b

To a stirring solution of cyclopropylmethylamine (0.870 mL, 10.0 mmol) and NEt_3 (3.50 mL, 25.0 mmol) in CH_2Cl_2 (33 mL), was added benzyl isocyanate (1.20 mL, 9.95 mmol). The reaction mixture was stirred for 2 h during which time a colourless solid had formed. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with aq. 1M HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL) before being dried over Na_2SO_4 and concentrated *in vacuo* to provide the title compound (1.87 g, 92%) as a colourless solid; m.p. 110–111 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3344 (m), 3301 (m), 1614 (s), 1571 (s), 1453 (m), 1242 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.21 (5H, m, 2 × C**7**-H, 2 × C**8**-H, C**9**-H), 5.10 (1H, br. m, N**2**-H), 4.87 (1H, br. m, N**1**-H), 4.31 (2H, d, *J* = 5.5 Hz, C**5**-H$_2$), 2.99 (2H, dd, *J* = 6.5, 4.5 Hz, C**3**-H$_2$), 0.89 (1H, m, C**2**-H), 0.43 (2H, m, 2 × C**1**-H$_2$), 0.12 (2H, m, 2 × C**1**-H$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.5 (C**4**), 139.5 (C**6**), 128.7, 127.6 (C**7**, C**8**), 127.3 (C**9**), 45.4 (C**3**), 44.6 (C**5**), 11.3 (C**2**), 3.4 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{12}H_{17}N_2O$: 205.1335. Found $[M + H]^+$: 205.1337.

1-Benzyl-5-ethyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one (268)



263b **268**

To a flame dried reaction tube equipped with a stir bar was added $[Rh(cod)_2]OTf$ (3.51 mg, 0.00750 mmol), PPh_3 (5.90 mg, 0.0225 mmol) and **263b** (30.6 mg, 0.150 mmol). The tube was sealed with a rubber septum and purged with argon for 30 minutes. Dry toluene (0.75 mL) was added by syringe and the reaction mixture was stirred for 10 seconds. The tube was sealed and heated at 140 °C for 20 h. The crude reaction mixture was concentrated *in vacuo* and purified by FCC (40% EtOAc/hexane) to provide the title compound (7.00 mg, 36% assuming 2 eq. of substrate required) as a pale yellow solid; ν_{max} / cm^{-1}: 3214 (w), 3085 (w), 2924 (m), 1697 (m), 1660 (s), 1450 (s), 1434 (s),

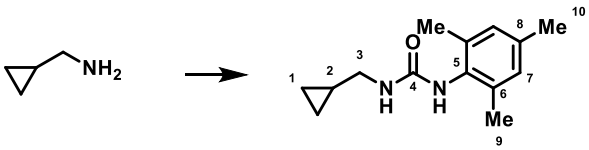
1277 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.32 (5H, m, 2 × C12-H, 2 × C13-H, C14-H), 5.67 (1H, t, *J* = 1.5 Hz, C**2**-H), 4.80 (1H, br. s, NH), 4.68 (1H, d, *J* = 15.5 Hz, C**10**-H), 4.54 (1H, d, *J* = 15.5 Hz, C**10**-H), 3.94 (1H, m, C**4**-H), 1.94 (2H, m, C**8**-H_2), 1.58–1.30 (4H, m, C**5**-H_2, C**6**-H_2), 0.98 (3H, t, *J* = 7.5 Hz, C**9**-H_3), 0.92 (3H, t, *J* = 7.5 Hz, C**7**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.5 (C**1**), 138.3 (C**11**), 128.7, 127.6 (C**12**, C**13**), 127.4 (C**14**), 122.6 (C**2**), 116.7 (C**3**), 54.8 (C**4**), 49.6 (C**10**), 37.9 (C**5**), 23.5 (C**8**), 17.3 (C**6**), 14.1 (C**7**), 12.1 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{16}H_{23}N_2O$: 259.1805. Found $[M + H]^+$: 259.1801.

1-(*tert*-Butyl)-3-(cyclopropylmethyl)urea (263c)

263c

To a stirring solution of cyclopropylmethylamine (0.870 mL, 10.0 mmol) in CH_2Cl_2 (33 mL), was added *tert*-butyl isocyanate (1.08 mL, 9.50 mmol). The reaction was stirred for 2 h during which time a colourless solid formed. The suspension was diluted with CH_2Cl_2 (100 mL) and washed with aq. 1M HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL) before being dried over Na_2SO_4 and concentrated *in vacuo* to provide the title compound (1.21 g, 75%) as a colourless solid; m.p. 147–149 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3355 (m), 3317 (m), 2963 (m), 1629 (s), 1559 (s), 1269 (m), 1216 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.55 (1H, br. m, N**1**-H), 4.46 (1H, br. s, N**2**-H), 2.98 (2H, dd, *J* = 6.5, 5.5 Hz, C**3**-H_2), 1.32 (9H, s, C**6**-H_3), 0.92 (1H, m, C**2**-H), 0.45 (2H, m, 2 × C**1**-H_2), 0.15 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.8 (C**4**), 50.4 (C**5**), 45.3 (C**3**), 29.7 (C**6**), 11.3 (C**2**), 3.4 (C**1**); HRMS: (ESI$^+$) Calculated for $C_9H_{19}N_2O$: 171.1492. Found $[M + H]^+$: 171.1495.

1-(Cyclopropylmethyl)-3-mesitylurea (263d)

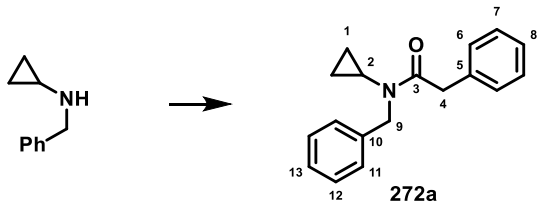


263d

To a stirring solution of cyclopropylmethylamine (0.870 mL, 10.0 mmol) in CH_2Cl_2 (20 mL), was added mesityl isocyanate (1.53 g, 9.50 mmol). The reaction was stirred for 2 h during which time a colourless solid formed. The suspension was diluted with CH_2Cl_2 (200 mL) and washed with aq. 1M HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL) before being dried over Na_2SO_4 and concentrated *in vacuo* to provide the title compound (1.73 g, 78%) as a colourless solid; m.p. 206–208 °C ($CHCl_3$); ν_{max} / cm^{-1}: 3318 (m), 2919 (w), 1631 (s), 1609 (m), 1563 (s), 1519 (m), 1476 (m), 1237 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.93 (2H, s, 2 × C**7**-H), 5.73 (1H, br. s, N**2**-H), 4.36 (1H, br. m, N**1**-H), 3.06 (2H, dd, *J* = 6.5, 6.0 Hz, C**3**-H_2), 2.29 (3H, s, C**10**-H_3), 2.25 (6H, s, C**9**-H_3), 0.89 (1H, m, C**2**-H), 0.41 (2H, m, 2 ×

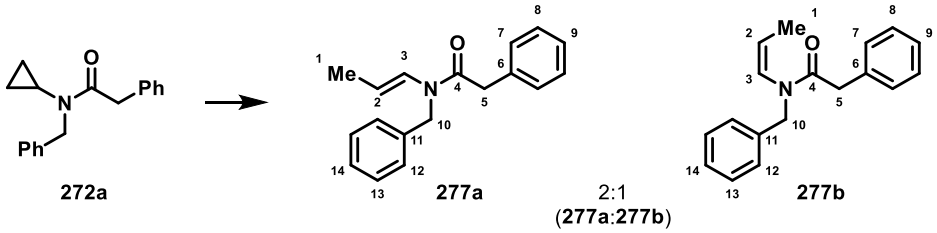
C**1**-H$_2$), 0.12 (2H, m, 2 × C**1**-H$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.2 (C**4**), 137.8 (C**8**), 137.2 (C**6**), 131.4 (C**5**), 129.6 (C**7**), 45.0 (C**3**), 21.1 (C**10**), 18.3 (C**8**), 11.6 (C**2**), 3.3 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{14}H_{21}N_2O$: 233.1648. Found $[M + H]^+$: 233.1656.

***N*-Benzyl-*N*-cyclopropyl-2-phenylacetamide (272a)**



To a stirring solution of *N*-benzylcyclopropanamine[354] (294 mg, 2.00 mmol) and NEt_3 (0.56 mL, 4.00 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added phenylacetyl chloride (0.400 mL, 3.00 mmol) over 1 minute. The reaction was warmed to room temperature and stirred for 4 h before being quenched by the addition of water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, washed with 1 M aq. NaOH (10 mL), 1 M aq. HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* before purification by FCC (20% EtOAc/hexane) to provide the title compound **25a** (531 mg, 51%) as a colourless oil; ν_{max} / cm^{-1}: 3027 (w), 1648 (s), 1495 (m), 1453 (m), 1396 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.07 (10H, m, 2 × C**6**-H, 2 × C**7**-H, C**8**-H, 2 × C**11**-H, 2 × C**12**-H, C**13**-H), 4.62 (2H, s, C**9**-H$_2$), 3.97 (2H, s, C**4**-H$_2$), 2.47 (1H, m, C**2**-H), 0.84 (4H, m, 2 × C**1**-H$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.0 (C**3**), 138.4 (C**10**), 135.4 (C**5**), 129.3, 128.6, 128.5, 128.0, 127.2, 126.8 (C**6**, C**7**, C**8**, C**11**, C**12**, C**13**), 50.1 (C**9**), 41.6 (C**4**), 30.4 (C**2**), 9.7 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{20}NO$: 266.1539. Found $[M + H]^+$: 266.1549.

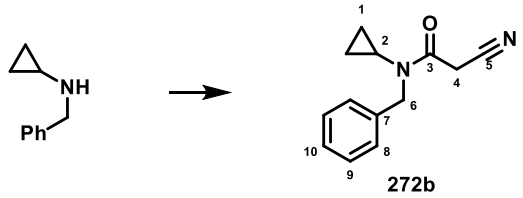
(*E*)-*N*-Benzyl-2-phenyl-*N*-(prop-1-en-1-yl)acetamide (277a) *and* (*Z*)-*N*-Benzyl-2-phenyl-*N*-(prop-1-en-1-yl)acetamide (277b)



To a flame dried reaction tube, equipped with a stir bar, was added $[Rh(cod)_2]BARF$ (8.87 mg, 7.50 μmol), PPh_3 (3.93 mg, 0.0150 mmol) and **25a** (39.8 mg, 0.150 mmol). The reaction tube was sealed with a rubber septum and purged with argon for 30 minutes. Dry 1,2-DCB (0.75 mL) was added by syringe and the reaction mixture was stirred for 10 seconds before being heated at 100 °C for 2 h. The reaction was transferred to a flask and concentrated *in vacuo* before being purified by FCC (25% EtOAc/hexane) to provide the title compounds (33.7 mg, 85% 2:1 mixture of diastereomers **277a** (A) and **277b** (B)) as a yellow oil; ν_{max} / cm^{-1}: 3285 (s), 3032 (w), 1636 (s), 1547 (s), 1491 (m), 1453 (m);

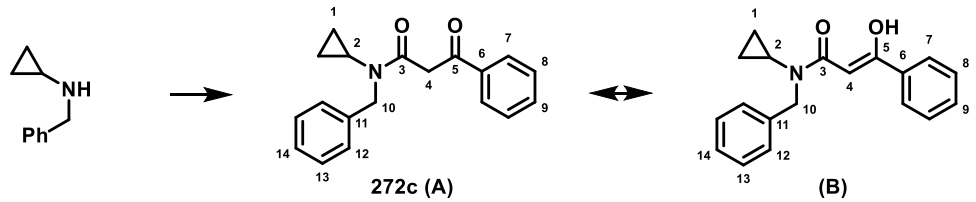
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42–7.14 (20H, m, 4 × C**7**-H, 4 × C**8**-H, 2 × C**9**-H, 4 × C**12**-H, 4 × C**13**-H, 2 × C**14**-H, A+B), 6.61 (1H, dd, *J* = 14.0, 1.5 Hz, C**3**-H, A), 6.00 (1H, dd, *J* = 7.5, 1.5 Hz, C**3**-H, B), 5.55 (1H, dq, *J* = 7.0, 6.0 Hz, C**2**-H, B), 5.05 (1H, dq, *J* = 14.0, 6.5 Hz, C**2**-H, A), 4.86 (2H, s, C**10**-H_2, A), 4.64 (2H, s, C**10**-H_2, B), 3.92 (2H, s, C**5**-H_2, A), 3.66 (2H, s, C**5**-H_2, B), 1.60 (3H, dd, *J* = 6.5, 1.5 Hz, C**1**-H_3, A), 1.41 (3H, dd, *J* = 7.0, 1.5 Hz, C**1**-H_3, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8 (C**4**, B), 169.9 (C**4**, A), 137.4 (C**11**, A), 137.2 (C**11**, B), 135.2 (C**6**, B), 134.6 (C**6**, A), 129.3 (ArC-H), 128.9 (C**3**, B), 128.7, 128.7, 128.4, 128.4, 128.3 (ArC-H), 128.1 (C**3**, A), 127.3, 127.1, 127.0, 126.9, 126.6, 125.5 (ArC-H), 110.7 (C**2**, A), 50.6 (C**10**, B), 47.4 (C**10**, A), 41.3 (C**5**, A), 40.9 (C**5**, B), 15.6 (C**1**, A), 12.2 (C**1**, B); HRMS: (ESI$^+$) Calculated for $C_{18}H_{20}NO$: 266.1539. Found $[M + H]^+$: 266.1549.

***N*-Benzyl-2-cyano-*N*-cyclopropylacetamide (272b)**



To a stirring solution of cyanoacetic acid (391 mg, 4.60 mmol) and *N*-benzylcyclopropanamine (615 mg, 4.18 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added a solution of DCC (906 mg, 4.39 mmol) and DMAP (26.0 mg, 0.210 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was warmed to room temperature and stirred for 4 h before being filtered over a short pad of celite. The filtrate was concentrated *in vacuo* and purified by FCC (25% EtOAc/hexane) to provide the title compound (476 mg, 53%) as a colourless solid; m.p. 56–58 °C (CH_2Cl_2); ν_{max} / cm^{-1}: 3029 (w), 1649 (s), 1417 (m), 1249 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.25 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 4.61 (2H, s, C**6**-H_2), 3.73 (2H, s, C**4**-H_2), 2.63 (1H, m, C**2**-H), 0.95 (2H, m, 2 × C**1**-H_2), 0.85 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.6 (C**3**), 137.1 (C**7**), 128.9, 128.1, 127.8 (C**8**, C**9**, C**10**), 114.3 (C**5**), 50.7 (C**6**), 30.4 (C**2**), 26.0 (C**4**), 9.5 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{15}N_2O$: 215.1179. Found $[M + H]^+$: 215.1179.

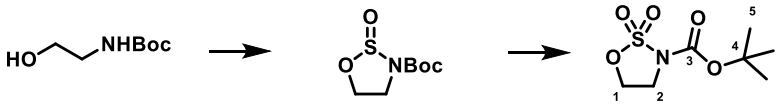
***N*-Benzyl-*N*-cyclopropyl-3-oxo-3-phenylpropanamide (272c)**



A solution of *N*-benzylcyclopropanamine (353 mg, 2.40 mmol), ethyl benzoylacetate (0.340 mL, 2.00 mmol) and DMAP (1.22 g, 10.0 mmol) in toluene (20 mL) was heated at reflux for 18 h. The

reaction mixture was cooled to room temperature and concentrated *in vacuo* before being redissolved in Et_2O (40 mL) and washed with 1 M aq. HCl (30 mL), water (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* and purified by FCC (10% EtOAc/hexane) to provide the title compound (532 mg, 91%) as an orange oil; ν_{max} / cm^{-1}: 2983 (w), 1622 (s), 1567 (s), 1460 (s), 1434 (s), 1358 (s), 1211 (s), 767 (s); *The product appears as a 4:5 mixture of tautomers (A:B) in $CDCl_3$ at room temperature:* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 15.15 (1H, s, O<u>H</u>, B), 7.98 (2H, d, *J* = 8.0 Hz, 2 × C**7**-<u>H</u>, A), 7.82 (2H, d, *J* = 7.0 Hz, 2 × C**7**-<u>H</u>, B), 7.60 (1H, m, C**9**-<u>H</u>, A), 7.50–7.40 (5H, m, 4 × C**8**-<u>H</u> (A+B), 1 × C**9**-<u>H</u> (B)), 7.35–7.24 (10H, m, 4 × C**12**-<u>H</u>, (A+B), 4 × C**13**-<u>H</u> (A+B), 2 × C**14**-<u>H</u>, (A+B)), 6.31 (1H, s, C**4**-<u>H</u>, B), 4.71 (2H, s, C**10**-<u>H_2</u>, B), 4.67 (2H, s, C**10**-<u>H_2</u>, A), 4.36 (2H, s, C**4**-<u>H_2</u>, A), 2.67-2.58 (2H, m, 2 × C**2**-<u>H</u>, A+B), 0.95–0.78 (8H, m, C**1**-<u>H_2</u>, A+B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.5 (C**5**, A), 174.6 (C**3**, B), 171.3 (C**5**, B), 170.4 (C**3**, A), 138.1 (C**11**, B), 137.9 (C**11**, A), 136.7 (C**6**, A), 135.1 (C**6**, B), 133.6 (C**9**, A), 130.8, 128.8, 128.7, 128.6, 128.6, 128.0, 127.7, 127.3, 127.2 (C**7** (A), C**8** (A+B), C**9** (A+B), C**12** (A+B), C**13** (A+B), C**14** (A+B)), 126.1 (C**7**, B), 86.9 (C**4**, B), 50.1 (C**10**, A), 49.5 (C**10**, B), 46.5 (C**4**, A), 30.5, 29.7 (C**2**, A+B), 9.3, 9.3 (C**1**, A+B); HRMS: (ESI^+) Calculated for $C_{19}H_{20}NO_2$: 294.1489. Found $[M + H]^+$: 294.1489.

***tert*-Butyl 1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (283)**

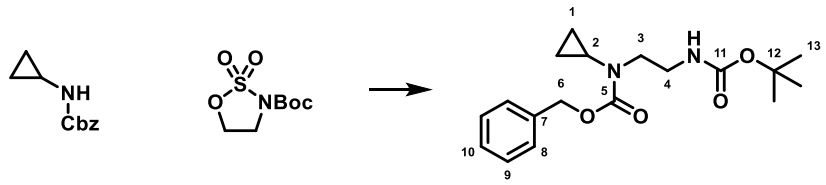


I **283**

*Hydroxycarbamate **I** was prepared according to a literature procedure[360]. The synthesis of sulfamidate **283** was carried out according to a literature procedure[361]*: To a flame dried three-necked flask fitted with a rubber septum and pressure equalising dropping funnel was added imidazole (8.90 g, 131 mmol) and the reaction vessel was sealed and placed under a nitrogen atmosphere. Dry CH_2Cl_2 (327 mL) was added by cannula which was followed by NEt_3 (10.0 mL, 71.9 mmol) and thionyl chloride (2.60 mL, 36.0 mmol) and then the rubber septum was replaced with a thermometer. The reaction mixture was cooled to between -50 and -60 °C in a dry ice/acetone bath. Hydroxycarbamate **I** (1.61 g, 10.0 mmol) in CH_2Cl_2 (82 mL) was then added by dropping funnel over 30 minutes. The reaction mixture was warmed to room temperature and stirred for 16 h before being concentrated *in vacuo* to provide the crude sulfamidite **II** as a brown liquid. The crude sulfamidite was immediately dissolved in acetonitrile (77 mL) and cooled to 0 °C. Sodium periodate (2.31 g, 10.8 mmol), $RuCl_3$ (20.7 mg, 0.100 mmol) and water (63 mL) were added in single portions, and the reaction was stirred whilst following closely by TLC. On consumption of the sulfamidite (typically 15 min) the reaction was diluted with water (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organics were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (25% EtOAc/Hex, dry loaded on silica) provided the title compound (1.52 g, 68%) as a colourless solid; m.p. 116–118 °C

(CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 2989 (w), 1720 (s), 1370 (m), 1357 (s), 1343 (s), 1323 (s), 1151 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.60 (2H, t, *J* = 6.5 Hz, C**1**-$\underline{H}_2$), 4.04 (2H, t, *J* = 6.5 Hz, C**2**-$\underline{H}_2$), 1.55 (9H, s, C**5**-$\underline{H}_3$). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[361]

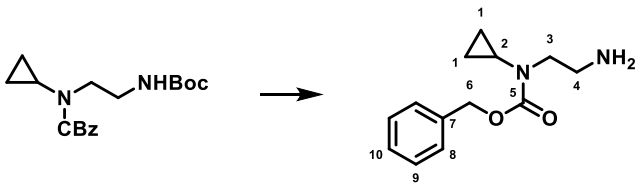
Benzyl (2-((*tert*-butoxycarbonyl)amino)ethyl)(cyclopropyl)carbamate (284a)



I **283** **284a**

*Cyclopropylcarbamate **I** was prepared according to a literature procedure*[102]: To a stirring solution of NaH (340 mg, 8.50 mmol, 60% suspension in mineral oil) in DMF (16.5 mL), at room temperature under an atmosphere of argon, was added cyclopropylcarbamate **I** (1.43 g, 7.50 mmol) in two portions over 2 minutes. The resulting suspension was stirred for 30 minutes during which time the solution became clear. Sulfamidate **283** (1.12 g, 5.00 mmol) was added to the reaction in two portions over 2 minutes at room temperature. The reaction mixture was stirred for 30 minutes before being concentrated *in vacuo*. The residue was redissolved in 1,4-dioxane (10 mL) and conc. HCl (4 mL) and stirred for 15 minutes. The reaction was neutralised by the addition of sat. aq. $NaHCO_3$ (30 mL) and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organics were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* before being purified by FCC (25% EtOAc/hexane) to provide the title compound (1.44 g, 86%) as a pale yellow oil which crystallised upon standing; m.p. 57–59 °C ($CHCl_3$); ν_{max} / cm^{-1}: 3354 (br.), 2975 (w), 2930 (w), 1691 (s), 1512 (m), 1409 (m), 1167 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.28 (5H, m, 2 × C**8**-$\underline{H}$, 2 × C**9**-$\underline{H}$, C**10**-$\underline{H}$), 5.14 (2H, s, C**6**-$\underline{H}_2$), 4.81 (1H, br. s, N$\underline{H}$), 3.40 (2H, m, C**3**-$\underline{H}_2$), 3.29 (2H, m, C**4**-$\underline{H}_2$), 2.65 (1H, m, C**2**-$\underline{H}$), 1.42 (9H, s, C**13**-$\underline{H}_3$), 0.78 (2H, m, 2 × C**1**-$\underline{H}_2$), 0.66 (2H, m, 2 × C**1**-$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.6 (C**5**), 156.1 (C**11**), 136.8 (C**7**), 128.6, 128.0, 127.8 (C**8**, C**9**, C**10**), 79.4 (C**12**), 67.3 (C**6**), 47.5 (C**3**), 39.7 (C**4**), 28.5 (C**13**), 8.2 (C**1**); HRMS: (ESI^+) Calculated for $C_{18}H_{26}N_2NaO_4$: 357.1785. Found $[M + Na]^+$: 357.1803.

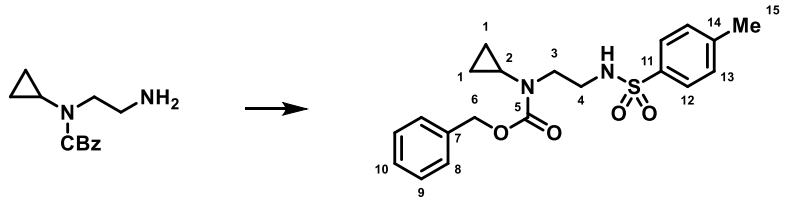
Benzyl (2-aminoethyl)(cyclopropyl)carbamate (284b)



284a **284b**

To a stirring solution of carbamate **284a** (1.44 g, 4.31 mmol) in CH_2Cl_2 (5.0 mL) was added trifluoroacetic acid (3.20 mL, 43.1 mmol) and the reaction was stirred for 1 h at room temperature. The reaction was diluted with CH_2Cl_2 (50 mL) before the addition of sat. aq. $NaHCO_3$ (50 mL). The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to provide the title compound (965 mg, 96%) as a yellow oil; ν_{max} / cm^{-1}: 3323 (br.), 2958 (s), 1689 (s), 1454 (m), 1413 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.27 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 5.15 (2H, s, C**6**-H_2), 3.35 (2H, t, *J* = 6.5 Hz, C**3**-H_2), 2.88 (2H, t, *J* = 6.5 Hz, C**4**-H_2), 2.62 (1H, tt, *J* = 7.0, 4.0 Hz, C**2**-H), 1.64 (2H, br. s, NH_2), 0.83–0.74 (2H, m, 2 × C**1**-H_2), 0.69–0.61 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.4 (C**5**), 136.7 (C**7**), 128.5, 128.5, 127.9 (C**8**, C**9**, C**10**), 67.2 (C**6**), 52.9 (C**3**), 40.5 (C**4**), 30.1 (C**2**), 8.1 (C**1**); HRMS: (ESI^+) Calculated for $C_{13}H_{19}N_2O_2$: 235.1441. Found $[M + H]^+$: 235.1450.

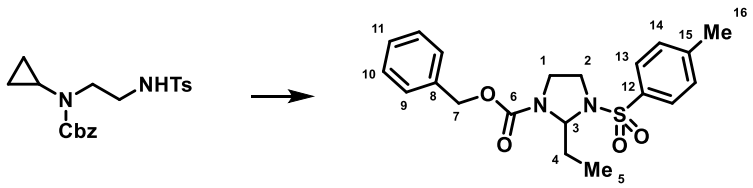
Benzyl cyclopropyl(2-((4-methylphenyl)sulfonamido)ethyl)carbamate (284c)



284b **284c**

To a stirring solution of amine **284b** (460 mg, 1.96 mmol) and NEt_3 (0.330 mL, 2.35 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (448 mg, 2.35 mmol). The reaction was stirred for 16 h before being quenched by the addition of water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% EtOAc/hexane) provided the title compound (442 mg, 50%) as a colourless oil; ν_{max} / cm^{-1}: 3249 (br.), 1683 (s), 1411 (m), 1329 (m), 1302 (m), 1156 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.68 (2H, d, *J* = 8.0 Hz, 2 × C**12**-H), 7.42–7.29 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 7.25 (2H, d, *J* = 8.0 Hz, 2 × C**13**-H), 5.13 (2H, s, C**6**-H_2), 5.03 (1H, br. s, NH), 3.39 (2H, t, *J* = 6.0 Hz, C**3**-H_2), 3.12 (2H, dt, *J* = 6.0, 6.0 Hz, C**4**-H_2), 2.50 (1H, tt, *J* = 7.0, 4.0 Hz, C**2**-H), 2.40 (3H, s, C**15**-H_3), 0.73 (2H, m, 2 × C**1**-H_2), 0.55 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.0 (C**5**), 143.5 (C**11**), 137.1 (C**14**), 136.6 (C**7**), 129.8 (C**13**), 128.7, 128.2, 127.9 (C**8**, C**9**, C**10**), 127.2 (C**12**), 67.5 (C**6**), 47.6 (C**3**), 42.6 (C**4**), 29.6 (C**2**), 21.6 (C**15**), 8.2 (C**1**); HRMS: (ESI^+) Calculated for $C_{20}H_{25}N_2O_4S$: 389.1530. Found $[M + H]^+$: 389.1541.

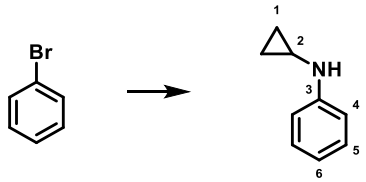
Benzyl (E)-(2-((4-methylphenyl)sulfonamido)ethyl)(prop-1-en-1-yl)carbamate (286c)



284c **286c**

General procedure B: [Rh(cod)$_2$]BARF (8.87 mg, 7.50 μmol), AsPh$_3$ (4.59 mg, 0.0150 mmol) and **284c** (58.3 mg, 0.150 mmol) were employed in 1,2-DCB (1.5 mL) at 140 °C for 24 h. Purification by FCC (30% EtOAc/hexane) provided the title compound (21.3 mg, 37%) as a pale yellow oil; ν_{max} / cm^{-1}: 2970 (br.), 2901 (br.), 1701 (s), 1411 (s), 1346 (s), 1163 (s); *The product appears as a 1:1 mixture of rotamers (A:B) in CDCl$_3$ at room temperature;* ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.71 (2H, d, *J* = 7.5 Hz, 2 × C**13**-H, A), 7.60 (2H, d, *J* = 7.5 Hz, 2 × C**13**-H, B), 7.43–7.33 (8H, m, 4 × C**9**-H, 4 × C**10**-H, A+B), 7.23–7.21 (4H, m, 2 × C**11**-H (A+B), 2 × C**14**-H (A)), 7.08 (2H, d, *J* = 7.5 Hz, 2 × C**14**-H, B), 5.42–5.32 (2H, m, 2 × C**3**-H, A+B), 5.11–4.91 (4H, m, 4 × C**7**-H$_2$, A+B), 3.75 (2H, m, 2 × C**1**/**2**-H$_2$, A/B), 3.53 (2H, m, 2 × C**1**/**2**-H$_2$, A/B), 3.18 (2H, m, 2 × C**1**/**2**-H$_2$, A/B), 2.91 (1H, m, C**1**/**2**-H$_2$, A/B), 2.76 (1H, m, C**1**/**2**-H$_2$, A/B), 2.37 (3H, s, C**16**-H$_3$, B), 2.33 (3H, s, C**16**-H$_3$, A), 1.81 (2H, m, C**4**-H$_2$, A/B), 1.64 (2H, m, C**4**-H$_2$, A/B), 1.00 (6H, m, C**5**-H$_3$, A+B); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 153.4, 153.0 (C**6**, A+B), 144.5, (C**15**, B), 144.3 (C**15**, A), 136.3, 136.3 (C**8**, A+B), 134.8 (C**12**, A), 134.5 (C**12**, B), 130.0, 130.0 (C**15**, A+B), 128.8, 128.6, 128.5, 128.4, 128.3, 128.0, (C**9**, C**10**, C**11**, A+B), 127.7 (C**14**, A), 127.4 (C**14**, B), 75.6, 74.9 (C**3**, A+B), 67.5, 67.0 (C**7**, A+B), 45.9, 45.1, 43.6, 43.4 (C**1**, C**2**, A+B), 28.3, 27.7 (C**4**, A+B), 21.7, 21.7, (C**16**, A+B), 9.5, 9.4 (C**5**, A+B). HRMS: (ESI$^+$) Calculated for $C_{20}H_{24}N_2NaO_4S$: 411.1354. Found [M + Na]$^+$: 411.1380.

***N*-Cyclopropylaniline (301)**

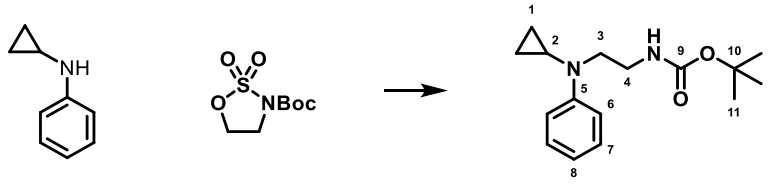


301

$Pd_2(dba)_3$ (45.7 mg, 0.0500 mmol), *rac*-BINAP (93.4 mg, 0.150 mmol) and sodium pentoxide (826 mg, 7.50 mmol) were added to a flame dried sealable reaction tube which was then fitted with a rubber septum and purged with argon. Degassed toluene (10 mL) was added followed by cyclopropylamine (0.550 mL, 8.00 mmol) and bromobenzene (0.530 mL, 5.00 mmol). The rubber septum was quickly replaced with a screw cap and the sealed reaction tube was heated at 130 °C for 16 h. The reaction mixture was cooled to room temperature before being filtered through a short pad of celite and concentrated *in vacuo*. Purification by FCC (3% EtOAc/hexane) provided the title compound (433 mg,

65%) as a bright orange oil; ν_{max} / cm^{-1}: 3389 (br.), 3009 (s), 1601 (s), 1501 (s), 1364 (m), 1312 (s), 1266 (m), 1019 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (2H, m, 2 × C**5**-H), 6.80 (2H, m, 2 × C**4**-H), 6.75 (1H, m, C**6**-H), 4.16 (1H, br. s, NH), 2.43 (1H, m, C**2**-H), 0.74 (2H, m, 2 × C**1**-H_2), 0.52 (2H, m, 2 × C**1**-H_2). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[362]

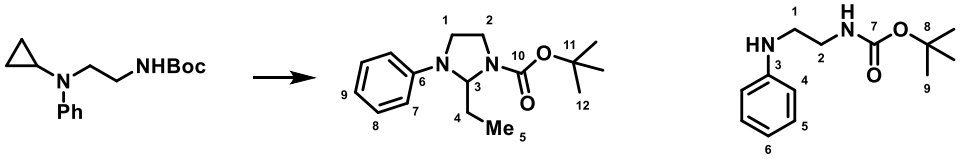
***tert*-Butyl (2-(cyclopropyl(phenyl)amino)ethyl)carbamate (302a)**



301 **283** **302a**

N-Cyclopropylaniline (1.20 g, 9.0 mmol) and THF (20 mL) were transferred to a flask under an atmosphere of N_2 which was then cooled to -78 °C. *n*-BuLi (6.50 mL, 1.6 M, 10.5 mmol) was added dropwise over 30 minutes, forming an orange suspension. The reaction was stirred for 15 minutes before the addition of sulfamidate **283** (1.67 g, 7.5 mmol) in THF (15 mL) dropwise over 10 minutes, which caused the formation of an orange homogenous solution. After a further 15 minutes the reaction was warmed to room temperature and quenched with 2 M aq. HCl (20 mL) then stirred for a further 30 minutes. The biphasic solution was neutralised with sat. aq. $NaHCO_3$ (100 mL), separated and the aqueous layer was further extracted with Et_2O (2 × 50 mL). The combined organics were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% EtOAc/hexane) provided the title compound (1.67 g, 81%) as an orange oil; ν_{max} / cm^{-1}: 3347 (br.), 2975 (w), 1694 (s), 1598 (m), 1500 (s), 1366 (s), 1248 (m), 1169 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (2H, m, 2 × C**7**-H), 7.01 (2H, m, 2 × C**6**-H), 6.76 (1H, t, *J* = 7.5 Hz, C**8**-H), 4.58 (1H, s, NH), 3.53 (2H, t, *J* = 6.5 Hz, C**3**-H_2), 3.32 (2H, m, C**4**-H_2), 2.48 (1H, tt, *J* = 7.0, 4.0 Hz, C**2**-H), 1.43 (9H, s, C**11**-H_3), 0.84 (2H, m, 2 × C**1**-H_2), 0.61 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0 (C**9**), 149.5 (C**5**), 129.1 (C**7**), 117.8 (C**8**), 114.3 (C**6**), 79.4 (C**10**), 51.0 (C**3**), 38.6 (C**4**), 32.2 (C**2**), 28.5 (C**11**), 9.3 (C**1**); HRMS: (ESI^+) Calculated for $C_{16}H_{25}N_2O_2$: 277.1911. Found $[M + H]^+$: 277.1918.

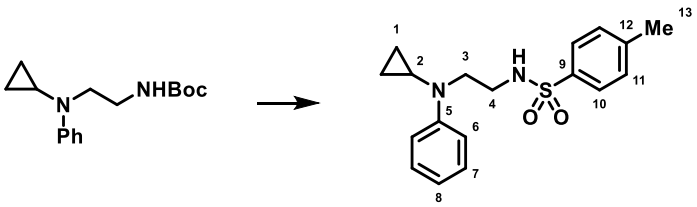
***tert*-Butyl 2-ethyl-3-phenylimidazolidine-1-carboxylate (304a) *and tert*-Butyl (2-(phenylamino)ethyl)carbamate (I)**



302a **304a** **I**

General procedure B: [Rh(cod)$_2$]BARF (13.3 mg, 0.0113 mmol), PPh_3 (5.90 mg, 0.0225 mmol) and **302a** (41.5 mg, 0.150 mmol) were employed in 1,2-DCB (1.5 mL) at 150 °C for 18 h. Purification by FCC (10–30% EtOAc/hexane) provided **304a** (21.5 mg, 52%) as an orange oil and decyclopropanated product **I** (1.9 mg, 5%) as a colourless oil; **Data for major compound 304a:** ν_{max} / cm^{-1}: 2971 (br.), 1696 (s), 1599 (m), 1505 (m), 1406 (s), 1365 (s), 1335 (s); *The compound appears as a 1:1 mixture of rotamers (A/B) in $CDCl_3$ at room temperature*; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (4H, m, 4 × C**8**-H, A+B), 6.76 (2H, t, *J* = 7.5 Hz, 2 × C**9**-H, A+B), 6.62 (4H, d, *J* = 8.0 Hz, C**7**-H, A+B), 5.41–5.28 (2H, br. m, C**3**-H, A+B), 4.01–3.87 (2H, br. m, 2 × C**1**/**2**-H, A+B), 3.61–3.53 (4H, m, 2 × C**1**-H, 2 × C**2**-H, A+B), 3.46–3.42 (2H, br. m, 2 × C**1**/**2**-H, A+B), 1.94 (2H, br. m, C**4**-H$_2$, A/B), 1.80 (2H, br. m, C**4**-H$_2$, A/B), 1.49 (18H, s, 18 × C**12**-H$_3$, A+B), 0.87 (6H, br. m, 6 × C**5**-H$_3$, A+B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.5 (C**10**, A+B), 145.8 (C**6**, A+B), 129.4 (C**8**, A+B), 117.3 (C**9**, A+B), 112.9 (C**7**, A+B), 73.0 (C**3**, A+B), 46.2 (C**1**/**2**, A+B) 43.5 (C**1**/**2**, A+B), 28.6 (C**12**, A+B), 25.8 (C**4**, A+B), 8.5 (C**5**, A+B); HRMS: (ESI$^+$) Calculated for $C_{16}H_{25}N_2O_2$: 277.1911. Found [M + H]$^+$: 277.1913. **Data for minor compound I**: ν_{max} / cm^{-1}: 3366 (br.), 2975 (w), 1689 (s), 1602 (s), 1506 (s), 1366 (m), 1251 (s), 1167 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 (2H, m, 2 × C**5**-H), 6.71 (1H, t, *J* = 7.5 Hz, C**6**-H), 6.62 (2H, d, *J* = 8.0 Hz, C**4**-H), 4.79 (1H, br. s, NH), 3.37 (2H, m, C**2**-H$_2$), 3.26 (2H, t, *J* = 5.5 Hz, C**1**-H$_2$), 1.45 (9H, s, C**9**-H$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5 (C**7**), 147.9 (C**3**), 129.4 (C**5**), 117.8 (C**6**), 112.9 (C**4**), 79.7 (C**8**), 44.5 (C**1**), 40.2 (C**2**), 28.5 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{21}N_2O_2$: 237.1598. Found [M + H]$^+$: 237.1592.

***N*-(2-(Cyclopropyl(phenyl)amino)ethyl)-4-methylbenzenesulfonamide (302b)**

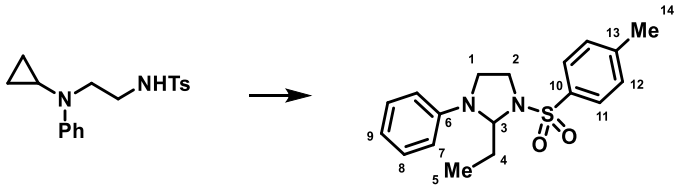


302a **302b**

Trifluoroacetic acid (5.6 mL, 73.4 mmol) was added to a stirring solution of carbamate **302a** (2.03 g, 7.34 mmol) in CH_2Cl_2 (24 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h before being concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (30 mL) and neutralised with sat. aq. $NaHCO_3$ (30 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to provide the crude diamine. The crude diamine and NEt_3 (1.19 mL, 8.51 mmol) were dissolved in CH_2Cl_2 (9.5 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (1.08 g, 5.67 mmol) was added in one portion and the reaction was warmed to room temperature and stirred for 3 h. The reaction mixture was diluted in CH_2Cl_2 (30 mL) and washed with water (30 mL) and brine (30 mL) before being dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (15% EtOAc/hexane) provided the title compound (371 mg, 15%) as a colourless oil; ν_{max} / cm^{-1}: 3285 (br.), 2955 (br.), 1599 (m), 1500 (m),

1327 (m), 1159 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (2H, d, *J* = 8.5 Hz, 2 × C**10**-H), 7.28 (2H, d, *J* = 8.5 Hz, 2 × C**11**-H), 7.20 (2H, m, 2 × C**7**-H), 6.91 (2H, m, 2 × C**6**-H), 6.78 (1H, m, C**8**-H), 4.55 (1H, t, *J* = 6.0 Hz, NH), 3.51 (2H, t, *J* = 7.0 Hz, C**3**-H_2), 3.14 (2H, td, *J* = 7.0, 6.0 Hz, C**4**-H_2), 2.42 (3H, s, C**13**-H_3), 2.38 (1H, m, C**2**-H), 0.79 (2H, m, C**1**-H), 0.52 (2H, m, C**1**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.2 (C**5**), 143.7 (C**12**), 137.0 (C**9**), 129.9 (C**11**), 129.2 (C**7**), 127.2 (C**10**), 118.5 (C**8**), 114.9 (C**6**), 51.6 (C**3**), 40.6 (C**4**), 32.2 (C**2**), 21.7 (C**13**), 9.2 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{23}N_2O_2S$: 331.1475. Found $[M + H]^+$: 331.1474.

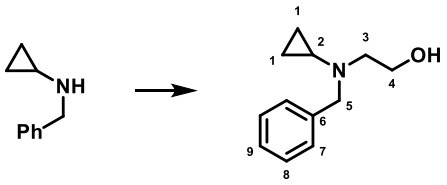
2-Ethyl-1-phenyl-3-tosylimidazolidine (304b)



302b **304b**

General procedure B: [Rh(cod)$_2$]BARF (13.3 mg, 0.0113 mmol), PPh_3 (5.90 mg, 0.0225 mmol) and **302b** (49.6 mg, 0.150 mmol) were employed in 1,2-DCB (1.5 mL) at 140 °C for 16 h. Purification by FCC (30% EtOAc/hexane) provided the title compound (18.4 mg, 37%) as a yellow oil; ν_{max} / cm^{-1}: 2969 (w), 1598 (m), 1504 (m), 1343 (s), 1162 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (2H, d, *J* = 8.5 Hz, 2 × C**11**-H), 7.16 (2H, m, 2 × C**8**-H), 7.04 (2H, d, *J* = 8.5 Hz, 2 × C**12**-H), 6.71 (1H, t, *J* = 7.5 Hz, C**9**-H), 6.32 (2H, d, *J* = 8.0 Hz, 2 × C**7**-H), 5.22 (1H, dd, *J* = 8.5, 3.5 Hz, C**3**-H), 3.85 (1H, ddd, *J* = 12.5, 8.0, 3.0 Hz, C**2**-H_2), 3.67 (1H, ddd, *J* = 12.5, 9.0, 7.5 Hz, C**2**-H_2), 3.16 (1H, ddd, *J* = 8.5, 7.5, 3.0 Hz, C**1**-H_2), 2.54 (1H, q, *J* = 8.5 Hz, C**1**-H_2), 2.28 (3H, s, C**14**-H_3), 1.87 (1H, dqd, *J* = 15.0, 7.5, 3.5 Hz, C**4**-H_2), 1.66 (1H, m, C**4**-H_2), 1.08 (3H, t, *J* = 7.5 Hz, C**5**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.3 (C**6**), 144.1 (C**13**), 134.9 (C**10**), 129.7 (C**12**), 129.2 (C**8**), 127.5 (C**11**), 117.4 (C**9**), 112.1 (C**7**), 77.0 (C**3**), 45.7 (C**2**), 45.5 (C**1**), 27.2 (C**4**), 21.6 (C**14**), 9.5 (C**5**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{23}N_2O_2S$: 331.1475. Found $[M + H]^+$: 331.1464.

2-(Benzyl(cyclopropyl)amino)ethan-1-ol (303)

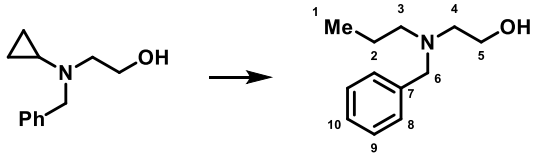


303

To a stirring solution of benzylcyclopropylamine (736 mg, 5.00 mmol) in THF (10 mL) under an atmosphere of argon was added ethylene oxide (4 ml, 10.0 mmol, 2.5-3.3 M in THF) followed by $ZnCl_2$ (136 mg, 1.0 mmol). The reaction was stirred for 19 h during which time a colourless precipitate had

formed. The suspension was diluted with Et_2O (30 mL) and washed with water (40 mL). The aqueous phase was further extracted with Et_2O (2 × 30 mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the title compound (800 mg, 84%) as a colourless oil; ν_{max} / cm^{-1}: 3384 (br.), 2923 (m), 2820 (m), 1495 (m), 1453 (s), 1350 (m), 1018 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.24 (5H, m, 2 × C**7**-H, 2 × C**8**-H, C**9**-H), 3.77 (2H, s, C**5**-H_2), 3.58 (2H, t, *J* = 5.5 Hz, C**4**-H_2), 2.75 (2H, t, *J* = 5.5 Hz, C**3**-H_2), 2.35 (1H, br. s, OH), 1.84 (1H, m, C**2**-H), 0.52 (2H, m, 2 × C**1**-H_2), 0.43 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.2 (C**6**), 129.5, 128.3 (C**7**, C**8**), 127.3 (C**9**), 59.9 (C**5**), 58.5 (C**4**), 56.5 (C**3**), 36.9 (C**2**), 7.4 (C**1**); HRMS: (ESI^+) Calculated for $C_{12}H_{18}NO$: 192.1383. Found $[M + H]^+$: 192.1378.

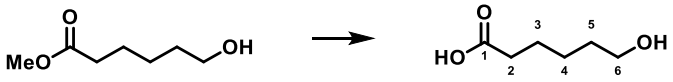
2-(Benzyl(propyl)amino)ethan-1-ol (307)



303 **307**

General procedure B: $[Rh(cod)_2]BARF$ (8.87 mg, 0.0075 mmol), PPh_3 (3.93 mg, 0.015 mmol) and **303** (28.7 mg, 0.150 mmol) were employed in 1,2-DCB (0.75 mL) at 120 °C for 15 h. Purification by FCC (20% EtOAc/hexane) provided the title compound (8.41 mg, 29%) as a colourless oil; ν_{max} / cm^{-1}: 3359 (br.), 2957 (m), 2872 (m), 1631 (m), 1453 (m), 1052 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.23 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 3.63 (2H, s, C**6**-H_2), 3.56 (2H, t, *J* = 5.5 Hz, C**5**-H_2), 2.64 (2H, t, *J* = 5.5 Hz, C**4**-H_2), 2.45 (2H, m, C**3**-H_2), 1.52 (2H, tt, *J* = 7.5, 7.5 Hz, C**2**-H_2), 0.87 (3H, t, *J* = 7.5 Hz, C**1**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.7 (C**7**), 129.1 128.5 (C**8**, C**9**), 127.3 (C**10**), 58.5 (C**6**), 58.5 (C**5**), 55.8 (C**3**), 55.3 (C**4**), 20.2 (C**2**), 11.9 (C**1**); HRMS: (ESI^+) Calculated for $C_{12}H_{20}NO$: 194.1539. Found $[M + H]^+$: 194.1546.

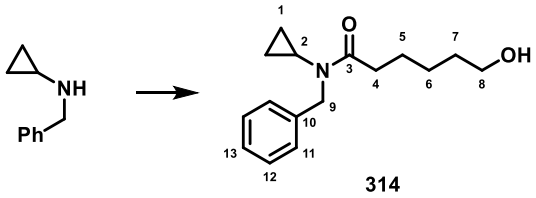
6-Hydroxyhexanoic acid



KOH pellets (6.70 g, 120 mmol) were added to a stirring solution of methyl 6-hydroxyhexanoate (6.40 g, 40.0 mmol) in MeOH (80 mL) in one portion. The reaction mixture was stirred for 4 h before being concentrated *in vacuo*. The residue was dissolved in EtOAc (200 mL) and 2 M aq. $NaHSO_4$ (200 mL). The organic layer as washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to provide 6-hydroxyhexanoic acid (4.90 g, 93%) as a colourless oil; ν_{max} / cm^{-1}: 3247 (br.), 2938 (m), 2522 (br.), 1675 (s), 1416 (m), 1303 (s), 1046 (s), 985 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.90 (1H, br. s, CH_2OH), 3.66 (2H, td, *J* = 6.5, 1.0 Hz, C**6**-H_2), 2.37 (2H, t, *J* = 7.5 Hz, C**2**-H_2), 1.67 (2H, m, C**3**-H_2), 1.59 (2H, m, C**5**-H_2), 1.42 (2H, m, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.2 (C**1**), 62.8

(C**6**), 34.0 (C**2**), 32.3 (C**5**), 25.3 (C**4**), 24.5 (C**3**); HRMS: (ESI$^+$) Calculated for $C_6H_{12}NaO_3$: 155.0679. Found [M + Na]$^+$: 155.0677.

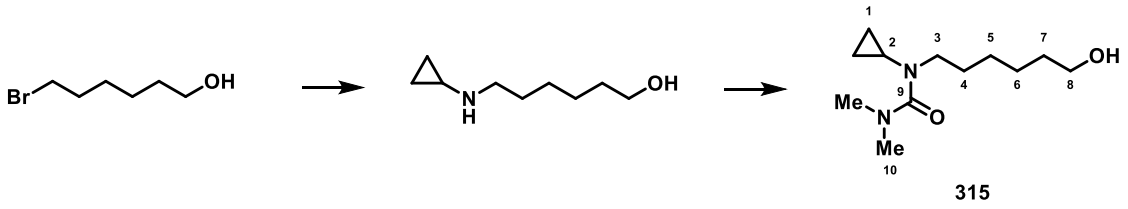
***N*-Benzyl-*N*-cyclopropyl-6-hydroxyhexanamide (314)**



314

EDCI (2.20 g, 11.5 mmol) and DMAP (122 mg, 1.0 mmol) were added to a flask which was sealed with a rubber septum and purged with argon for 10 minutes. CH_2Cl_2 (20 mL) and *N*-benzylcyclopropanamine (1.47 g, 10.0 mmol) were added by syringe and the mixture was cooled to 0 °C. 6-Hydroxyhexanoic acid (1.45 g, 11.0 mmol) in CH_2Cl_2 (5 mL) was added and the reaction mixture was warmed to room temperature and stirred for 16 h. The resulting solution was concentrated *in vacuo* and dissolved in water (40 mL) and EtOAc (40 mL). The organic layer was washed with 1 M aq. NaOH (20 mL), 1 M aq. HCl (20 mL) and brine (20 mL) before being dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (30% EtOAc/hexane) provided the title compound (2.19 g, 84%) as a colourless oil; ν_{max} / cm^{-1}: 3403 (br.), 2931 (m), 2860 (m), 1631 (s), 1409 (s), 1373 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.24 (5H, m, 2 × C**11**-H, 2 × C**12**-H, C**13**-H), 4.63 (2H, s, C**9**-H_2), 3.69 (2H, t, *J* = 6.5 Hz, C**8**-H_2), 2.62 (2H, t, *J* = 7.5 Hz, C**4**-H_2), 2.56 (1H, m, C**2**-H), 1.75 (2H, m, C**5**-H_2), 1.63 (2H, m, C**7**-H_2), 1.46 (2H, m, C**6**-H_2), 0.86 (2H, m, 2 × C**1**-H_2), 0.79 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1 (C**3**), 138.6 (C**10**), 128.6, 127.9 (C**11**, C**12**), 127.1 (C**13**), 62.7 (C**8**), 49.9 (C**9**), 34.2 (C**4**), 32.6 (C**7**), 30.1 (C**1**), 25.7 (C**6**), 24.7 (C**5**), 9.4 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{16}H_{24}NO_2$: 262.1802. Found [M + H]$^+$: 262.1801.

1-Cyclopropyl-1-(6-hydroxyhexyl)-3,3-dimethylurea (315)

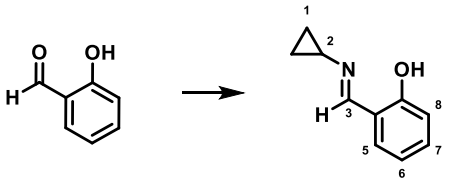


315

A stirring solution of cyclopropylamine (0.69 mL, 10 mmol), K_2CO_3 (1.04 g ,7.50 mmol) and 6-bromohexan-1-ol (905 mg, 5.00 mmol) in MeCN (10 mL) was heated at 80 °C for 16 h. The reaction mixture was dissolved in water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to yield the crude aminoalcohol intermediate as a pale brown oil which was carried through without further purification. To a stirring solution of crude aminoalcohol and NEt_3 (0.84 mL, 6.00 mmol) in CH_2Cl_2 (17 mL) at 0 °C under argon was added

dimethylcarbamoyl chloride (0.55 mL, 6.00 mmol). The reaction mixture was stirred for 3 h before being quenched by the addition of water (5 mL) and 1 M aq. HCl (20 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (5% MeOH/EtOAc) provided the title compound (361 mg, 32%) as a colourless oil; ν_{max} / cm^{-1}: 3392 (br.), 2928 (m), 2858 (m), 1613 (s), 1496 (m), 1400 (s), 1370 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.62 (2H, t, *J* = 6.5 Hz, C**8**-$\underline{H}_2$), 3.20 (2H, t, *J* = 7.5 Hz, C**3**-$\underline{H}_2$), 2.85 (6H, s, C**10**-$\underline{H}_3$), 2.57 (1H, m, C**2**-$\underline{H}$), 1.62–1.52 (4H, m, C**4**-$\underline{H}_2$, C**7**-$\underline{H}_2$), 1.41–1.27 (4H, m, C**5**-$\underline{H}_2$, C**6**-$\underline{H}_2$), 0.72 (2H, m, 2 × C**1**-$\underline{H}_2$), 0.56 (2H, m, 2 × C**1**-$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.4 (C**9**), 62.8 (C**8**), 49.0 (C**3**), 38.1 (C**10**), 32.8 (C**7**), 30.6 (C**2**), 28.1 (C**4**), 26.7 (C**5**), 25.5 (C**6**), 8.8 (C**1**); HRMS: (ESI^+) Calculated for $C_{12}H_{25}N_2O_2$: 229.1911. Found $[M + H]^+$: 229.1900.

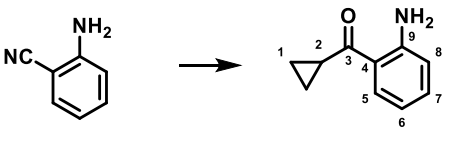
(*E*)-2-((Cyclopropylimino)methyl)phenol (316a)



316a

Cyclopropylamine (0.35 mL, 5.10 mmol) was added to a stirring solution of salicylaldehyde (0.53 mL, 5.00 mmol) in EtOH (5 mL) at room temperature causing the immediate formation of a bright yellow colour. The reaction was stirred for 16 h before being concentrated *in vacuo* and purified by FCC (5% EtOAc/hexane) to afford the title compound (780 mg, 97%) as an orange oil; ν_{max} / cm^{-1}: 2885 (w), 1621 (s), 1575 (m), 1487 (m), 1395 (m), 1271 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.75 (1H, s, O$\underline{H}$), 8.49 (1H, s, C**3**-$\underline{H}$), 7.26 (1H, m, C**7**-$\underline{H}$), 7.22 (1H, m, C**5**-$\underline{H}$), 6.93 (1H, d, *J* = 8.0 Hz, C**8**-$\underline{H}$), 6.87 (1H, m, C**6**-$\underline{H}$), 2.97 (1H, m, C**2**-$\underline{H}$), 1.00–0.94 (4H, m, 2 × C**1**-$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.1 (C**3**), 160.5 (C**9**), 131.7 (C**7**), 130.7 (C**5**), 119.2 (C**4**), 118.8 (C**6**), 116.9 (C**8**), 40.4 (C**2**), 9.5 (C**1**); HRMS: (ESI^+) Calculated for $C_{10}H_{12}NO$: 162.0913. Found $[M + H]^+$: 162.0920.

(2-Aminophenyl)(cyclopropyl)methanone

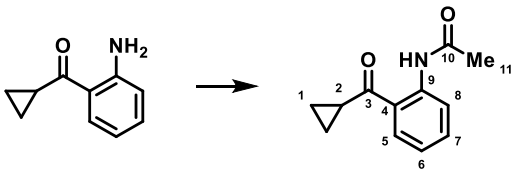


I

To a stirring solution of 2-aminobenzonitrile **323** (1.18 g, 10.0 mmol) in THF (20 mL) at 0 °C, under an atmosphere of argon, was added cyclopropylmagnesium bromide (60 mL, 30.0 mmol, 0.5 M in THF) dropwise over 30 minutes. The reaction was warmed to room temperature and stirred for 6 h before being quenched by the careful addition of 2 M aq. HCl (40 mL). The resulting biphasic solution was

stirred for 16 h before being basified by the addition of 4 M aq. NaOH (pH ~14). The organic layer was removed and the aqueous layer was further extracted with Et_2O (3 × 50 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% EtOAc/hexane) provided the title compound (451 mg, 28%) as a pale yellow oil; ν_{max} / cm^{-1}: 3461 (m), 3341 (m), 3005 (w), 1634 (m), 1614 (s), 1581 (s), 1547 (m), 1392 (m), 1222 (s), 1160 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96 (1H, d, *J* = 8.0 Hz, C**5**-H), 7.26 (1H, m, C**7**-H), 6.69 (1H, m, C**6**-H), 6.65 (1H, d, *J* = 8.5 Hz, C**8**-H), 6.13 (2H, br. s, NH_2), 2.64 (1H, m, C**2**-H), 1.17 (2H, m, 2 × C**1**-H_2), 0.96 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.0 (C**3**), 149.5 (C**9**), 133.9 (C**7**), 131.2 (C**5**), 119.2 (C**4**), 117.2 (C**8**), 115.9 (C**6**), 17.2 (C**2**), 10.7 (C**1**); HRMS: (ESI^+) Calculated for $C_{10}H_{12}NO$: 162.0913. Found $[M + H]^+$: 162.0915.

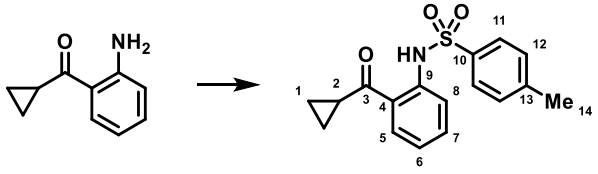
***N*-(2-(Cyclopropanecarbonyl)phenyl)acetamide (319a)**



I **319a**

To a stirring solution of aniline **I** (226 mg, 1.4 mmol) and NEt_3 (0.23 mL, 1.68 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added acetyl chloride (0.12 mL, 1.68 mmol). The reaction was stirred for 3 h before being quenched by the addition of water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (15% EtOAc/hexane) provided the title compound (215 mg, 75%) as a yellow oil; ν_{max} / cm^{-1}: 3249 (w), 1694 (m), 1639 (m), 1582 (s), 1519 (s), 1449 (s), 1379 (s), 1302 (s), 1208 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 11.54 (1H, br. s, NH), 8.69 (1H, d, *J* = 8.5 Hz, C**8**-H), 8.11 (1H, d, *J* = 8.0 Hz, C**5**-H), 7.54 (1H, dd, *J* = 8.5, 7.5 Hz, C**7**-H), 7.15 (1H, dd, *J* = 8.0, 7.5 Hz, C**6**-H), 2.69 (1H, m, C**2**-H), 2.20 (3H, s, C**11**-H_3), 1.26 (2H, m, 2 × C**1**-H_2), 1.09 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.4 (C**3**), 169.5 (C**10**), 140.3 (C**9**), 134.6 (C**7**), 130.9 (C**5**), 123.2 (C**4**), 122.5 (C**6**), 121.0 (C**8**), 25.7 (C**11**), 18.7 (C**2**), 12.3 (C**1**); HRMS: (ESI^+) Calculated for $C_{12}H_{14}NO_2$: 204.1019. Found $[M + H]^+$: 204.1008.

***N*-(2-(Cyclopropanecarbonyl)phenyl)-4-methylbenzenesulfonamide (319b)**



I **319b**

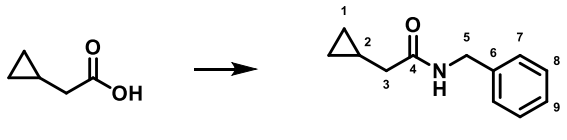
To a stirring solution of aniline **I** (226 mg, 1.40 mmol) and NEt_3 (0.46 mL, 3.36 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added *p*-toluenesulfonyl chloride (640 mg, 3.36 mmol). The reaction was stirred for 16 h before being quenched by the addition of water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% EtOAc/hexane) provided the title compound (222 mg, 50%) as a colourless oil; ν_{max} / cm^{-1}: 3008 (br. w), 1634 (m), 1492 (m), 1337 (m), 1159 (s), 1090 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.19 (1H, br. s, NH), 7.98 (1H, d, *J* = 8.0 Hz, C**5**-H), 7.68 (2H, d, *J* = 8.5 Hz, 2 × C**11**-H), 7.67 (1H, d, *J* = 8.5 Hz, C**8**-H), 7.45 (1H, dd, *J* = 8.5 ,7.5 Hz, C**7**-H), 7.21 (2H, d, *J* = 8.5 Hz, C**12**-H), 7.11 (1H, dd, *J* = 8.0 ,7.5 Hz, C**6**-H), 2.51 (1H, m, C**2**-H), 2.36 (3H, s, C**14**-H_3), 1.18 (2H, m, 2 × C**1**-H_2), 1.02 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.8 (C**3**), 143.8 (C**13**), 139.3 (C**9**), 136.8 (C**10**), 134.3 (C**7**), 131.0 (C**5**), 129.7 (C**12**), 127.4 (C**11**), 124.3 (C**4**), 123.0 (C**6**), 120.1 (C**8**), 21.7 (C**14**), 18.3 (C**2**), 12.5 (C**1**); HRMS: (ESI^+) Calculated for $C_{17}H_{18}NO_3S$: 316.1002. Found $[M + H]^+$: 316.1005.

2-Cyclopropylacetate (327)

326 **327**

KOH pellets (8.42 g, 150 mmol) were dissolved in water (100 mL) before the addition of cyclopropylacetonitrile **326** (9.11 mL, 100 mmol) at room temperature. The reaction mixture was heated at reflux for 5 h before being cooled to room temperature. The reaction mixture was washed with Et_2O (50 mL), acidified (pH 1) with conc. HCl and extracted with Et_2O (3 × 50 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to provide the title compound (10.6 g, 99%) as a colourless liquid; ν_{max} / cm^{-1}: 2918 (br.), 2675 (br.), 1708 (s), 1413 (m), 1222 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.41 (1H, br. s, OH), 2.27 (2H, d, *J* = 7.0 Hz, C**3**-H_2), 1.06 (1H, m, C**2**-H), 0.57 (2H, m, 2 × C**1**-H_2), 0.19 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.5 (C**4**), 39.2 (C**3**), 6.8 (C**2**), 4.5 (C**1**); HRMS: (Negative ion) Calculated for $C_5H_7O_2$: 99.0452. Found $[M - H]^-$: 99.0455.

***N*-Benzyl-2-cyclopropylacetamide (328a)**

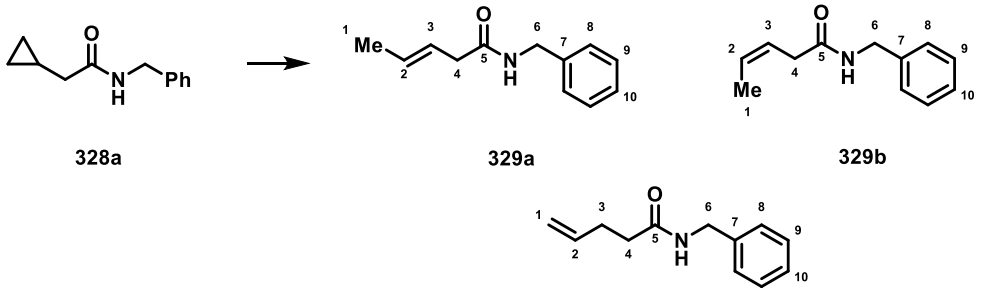


327 **328a**

To a stirring solution of carboxylic acid **327** (5.01 g, 50.0 mmol), DCC (11.3 g, 55.0 mmol) and DMAP (61 mg, 0.50 mmol) in dry CH_2Cl_2 (167 mL) at 0 °C was added benzylamine (5.73 mL, 52.5 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h before being filtered over a

short pad of celite. The filtrate was concentrated *in vacuo* and purified by FCC (40–50% EtOAc/hexane) to provide the crude product contaminated with dicyclohexylurea. The crude product was dissolved in the minimum amount of EtOAc and filtered to provide the title compound (4.40 g, 46%) as a colourless solid; m.p. (CH_2Cl_2/hexane); 56–58 °C; ν_{max} / cm^{-1}: 3298 (s), 3081 (w), 1632 (s), 1548 (s), 1452 (m), 1326 (m), 1229 (s), 1021 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.26 (5H, m, 2 × C**7**-H, 2 × C**8**-H, C**9**-H), 6.18 (1H, br. s, NH), 4.49 (2H, d, *J* = 5.5 Hz, C**5**-H_2), 2.21 (2H, d, *J* = 7.0 Hz, C**3**-H_2), 0.98 (1H, m, C**2**-H), 0.61 (2H, m, 2 × C**1**-H_2), 0.21 (2H, m, 2 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4 (C**4**), 138.6 (C**6**), 128.9 (C**8**), 127.8 (C**7**), 127.6 (C**9**), 43.6 (C**5**), 41.7 (C**3**), 7.3 (C**2**), 4.8 (C**1**); HRMS: (ESI^+) Calculated for $C_{12}H_{16}NO$: 190.1226. Found $[M + H]^+$: 190.1230.

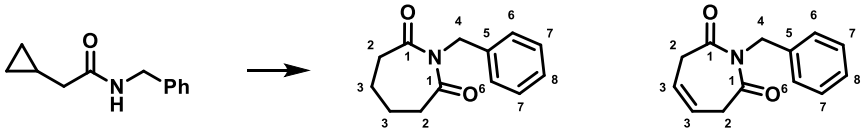
(*E*)-*N*-Benzylpent-3-enamide (329a) *and* (*Z*)-*N*-Benzylpent-3-enamide (329b) *and* *N*-Benzylpent-4-enamide (329c)



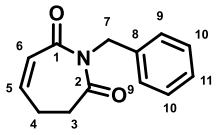
328a **329a** **329b** **329c**

General procedure B: $[Rh(cod)_2]BARF$ (8.87 mg, 0.0113 mmol), PPh_3 (3.93 mg, 0.0225 mmol) and **328a** (28.4 mg, 0.150 mmol) were employed in 1,4-dioxane (1.5 mL) at 120 °C for 24 h. Purification by FCC (20% EtOAc/hexane) provided **329a**, **329b** and **329c** (20.2 mg, 71%, 3:1.4:1 mixture of regioisomers and diastereomers A:B:C) as a pale yellow oil; **Data for the mixture of compounds 329a (A), 329b (B) and 329c (C):** ν_{max} / cm^{-1}: 3287 (s), 2917 (w), 1636 (s), 1543 (s), 1453 (m), 1235 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.25 (15H, m, 6 × C**8**-H, 6 × C**9**-H, 3 × C**10**-H, A+B+C), 5.94 (1H, br. s, NH, B), 5.89 (1H, br. s, NH, A), 5.89–5.51 (6H, m, 1 × NH (C), 3 × C**2**-H (A+B+C), 2 × C**3**-H (A+B)), 5.07 (1H, dq, *J* = 17.0, 1.5 Hz, C**1**-H, C), 5.01 (1H, dq, *J* = 10.0, 1.5 Hz, C**1**-H, C), 4.45 (6H, m, 6 × C**6**-H_2, A+B+C), 3.08 (2H, d, *J* = 7.5 Hz, C**4**-H_2, B) 2.99 (2H, d, *J* = 7.0 Hz, C**4**-H_2, A), 2.43 (2H, m, C**3**-H_2, C), 2.31 (2H, m, C**4**-H_2, C), 1.72 (3H, dd, *J* = 6.0, 1.5 Hz, C**1**-H_3, A), 1.65 (3H, m, C**1**-H_3, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.2 (C**5**, C), 171.3 (C**5**, A), 171.2 (C**5**, B), 138.5, 138.4, 137.2 (C**7**, A+B+C), 131.4, 130.0, (C**2**/**3**, A), 129.7 (C**2**/**3**, B), 128.9, 127.9, 127.8, 127.6 (ArC-H, A+B+C), 123.8 (C**2**/**3**, A), 122.7 (C**2**/**3**, B), 115.8 (C**1**, C), 43.8, 43.8, 43.7 (C**6**, A+B+C), 40.7 (C**4**, A), 36.0 (C**4**, C), 35.0 (C**4**, B), 29.8 (C**3**, C), 18.2 (C**1**, A), 13.1 (C**1**, B); HRMS: (ESI^+) Calculated for $C_{13}H_{16}NO_2$: 218.1176. Found $[M + H]^+$: 218.1176.

1-Benzyl-3,6-dihydro-1*H*-azepine-2,7-dione (331a) ***and*** **1-Benzylazepane-2,7-dione (330a)** ***and*** **1-Benzyl-3,4-dihydro-1*H*-azepine-2,7-dione (C)**



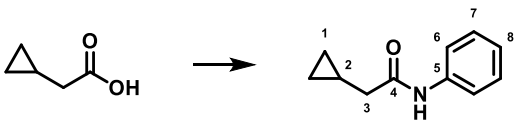
328a 330a 331a



C

General procedure B: [Rh(cod)$_2$]BARF (8.87 mg, 0.0075 mmol), P(C_6F_5)$_3$ (7.98 mg, 0.015 mmol), **60a** (28.4 mg, 0.150 mmol) and pyridine (0.015 mL, 0.5 M stock solution in 1,2-DCB) were employed in 1,2-DCB (2.0 mL) at 130 °C for 46 h. Purification by FCC (25% EtOAc/hexane) provided **330a** and **331a** (31.1 mg, 95%, 5.7:1, **330a**:**331a**) as a colourless oil; *Separated samples of **330a** and **331a** could be obtained by FCC (20% EtOAc/hexane); **C** is typically formed in >5% yield as determined by ^{1}H NMR analysis of the crude reaction against 1,4-DCB as an internal standard.* **Data for "saturated" compound 330a:** ν_{max} / cm^{-1}: 2948 (br.), 1710 (m), 1658 (s), 1339 (m), 1161 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.19 (5H, m, 2 × C**6**-H, 2 × C**7**-H, C**8**-H), 4.91 (2H, s, C**4**-H_2), 2.77 (4H, m, 4 × C**2**-H_2), 1.85 (4H, m, 4 × C**3**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.8 (C**1**), 137.9 (C**8**), 128.5, 128.5, 127.4 (C**6**, C**7**, C**8**), 46.5 (C**4**), 36.2 (C**2**), 20.8 (C**3**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{16}NO_2$: 218.1176. Found [M + H]$^+$: 218.1176. **Data for "unsaturated" compound 331a:** ν_{max} / cm^{-1}: 3032 (w), 1708 (m), 1659 (s), 1322 (m), 1227 (m), 1154 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27–7.18 (5H, m, 2 × C**6**-H, 2 × C**7**-H, C**8**-H), 6.03 (2H, t, *J* = 5.0 Hz, 2 × C**3**-H), 4.95 (2H, s, C**4**-H_2), 3.55 (4H, d, *J* = 5.0 Hz, 4 × C**2**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6 (C**1**), 137.7 (C**5**), 128.4 (C**6**), 128.3 (C**7**), 127.3 (C**8**), 126.0 (C**3**), 45.6 (C**4**), 38.9 (C**2**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{14}NO_2$: 216.1019. Found [M + H]$^+$: 216.1025. **Data for the minor product C:** *(Characteristic signals only)* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.63 (1H, dt, *J* = 12.0, 5.0 Hz, C**5**-H), 6.16 (1H, d, *J* = 12.0 Hz, C**6**-H), 4.95 (2H, s, C**7**-H_2), 2.88 (2H, m, C**3**-H_2), 2.54 (2H, m, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.2 (C**2**), 170.6 (C**1**), 144.5 (C**5**), 137.7 (C**8**), 127.8 (C**6**), 45.6 (C**7**), 37.6 (C**3**), 24.6 (C**4**);

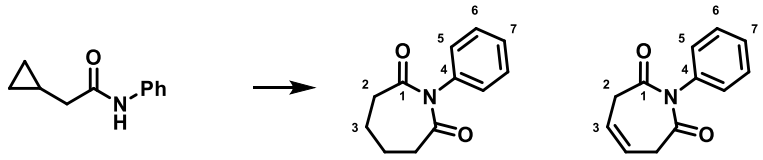
2-Cyclopropyl-*N*-phenylacetamide (328b)



327 328b

To a flame dried flask containing EDCI (1.05 g, 5.50 mmol) and DMAP (61.1 mg, 0.50 mmol) under an atmosphere of argon was added CH_2Cl_2 (10 mL) and aniline (0.46 mL, 5.00 mmol). The flask was cooled to 0 °C before the addition of carboxylic acid **327** (551 mg, 5.50 mmol). The reaction mixture was stirred for 66 h before being concentrated *in vacuo*. The resulting solid dissolved in 1 M aq. NaOH (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with 1 M aq. HCl (30 mL), dried over $MgSO_4$ before being concentrated *in vacuo*. Purification by FCC (20% EtOAc/hexane) provided the title compound (703 mg, 80%) as a colourless solid; m.p. (CH_2Cl_2/hexane); 100–101 °C; ν_{max} / cm^{-1}: 3246 (w), 1656 (s), 1596 (s), 1540 (s), 1442 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (1H, br. s, N<u>H</u>), 7.53 (2H, m, 2 × C**6**-<u>H</u>), 7.31 (2H, m, 2 × C**7**-<u>H</u>), 7.10 (1H, t, *J* = 8.0 Hz, C**8**-<u>H</u>), 2.31 (2H, d, *J* = 7.0 Hz, C**3**-<u>H_2</u>), 1.08 (1H, m, C**2**-<u>H</u>), 0.68 (2H, m, 2 × C**1**-<u>H_2</u>), 0.28 (2H, m, 2 × C**1**-<u>H_2</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8 (C**4**), 138.0 (C**5**), 129.1 (C**7**), 124.4 (C**8**), 120.0 (C**6**), 42.6 (C**3**), 7.4 (C**2**), 4.9 (C**1**); HRMS: (ESI^+) Calculated for $C_{11}H_{14}NO$: 176.1070. Found $[M + H]^+$: 176.1069.

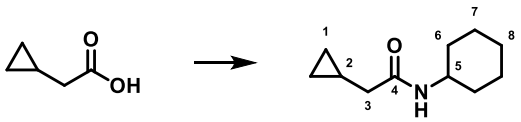
1-Phenylazepane-2,7-dione (330b) *and* 1-Phenyl-3,6-dihydro-1H-azepine-2,7-dione (331b)



328b **330b** **331b**

General procedure B: $[Rh(cod)_2]BARF$ (13.3 mg, 0.0113 mmol), $P(C_6F_5)_3$ (12.0 mg, 0.0225 mmol), **328b** (26.3 mg, 0.150 mmol) and pyridine (0.015 mL, 0.5 M stock solution in 1,2-DCB) were employed in 1,2-DCB (2.0 mL) at 130 °C for 46 h. Purification by FCC (50% EtOAc/hexane) provided the title compounds (6.7 mg, 22%, 2:1 A:B) as a pale yellow oil; **Data for the mixture of compounds 330b (A) and 331b (B):** ν_{max} / cm^{-1}: 2938 (w), 1715 (m), 1670 (s), 1491 (m), 1339 (m), 1248 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48–7.30 (6H, m, ArC<u>H</u>, A+B), 7.11–7.02 (4H, m, ArC<u>H</u>, A+B), 6.15 (2H, m, C**3**-<u>H</u>, B), 3.68 (4H, d, *J* = 4.5 Hz, C**2**-<u>H_2</u>, B), 2.93 (4H, m, C**2**-<u>H_2</u>, A), 2.04 (4H, m, C**3**-<u>H_2</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.9 (C**1**, A), 169.7 (C**1**, B), 138.4, 138.0 (C**4**, A+B), 129.4, 129.4, 128.5, 128.4, 128.4, 128.2, (Ar<u>C</u>H, A+B), 126.1 (C**3**, B), 39.2 (C**2**, B), 36.2 (C**2**, A), 20.9 (C**3**, A). **Data for the saturated product 330b:** δ; HRMS: (ESI^+) Calculated for $C_{12}H_{14}NO_2$: 204.1019. Found $[M + H]^+$: 204.1024: **Data for the unsaturated product 331b:** δ; HRMS: (ESI^+) Calculated for $C_{12}H_{12}NO_2$: 202.0863. Found $[M + H]^+$: 202.0863.

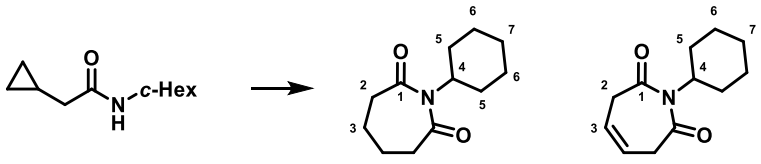
***N*-Cyclohexyl-2-cyclopropylacetamide (328c)**



327 **328c**

To a flame dried flask containing EDCI (1.05 g, 5.50 mmol) and DMAP (61.1 mg, 0.50 mmol) under an atmosphere of argon was added CH_2Cl_2 (10 mL) and cyclohexylamine (0.57 mL, 5.00 mmol). The flask was cooled to 0 °C before the addition of carboxylic acid **327** (551 mg, 5.50 mmol). The reaction mixture was stirred for 66 h before being concentrated *in vacuo*. The resulting solid dissolved in 1 M aq. NaOH (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with 1 M aq. HCl (30 mL), dried over $MgSO_4$ before being concentrated *in vacuo*. Purification by FCC (30% EtOAc/hexane) provided the title compound (413 mg, 46%) as a colourless solid; m.p. (CH_2Cl_2/hexane); 92–94 °C; ν_{max} / cm^{-1}: 3291 (m), 2978 (s), 2852 (m), 1632 (s), 1551 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.77 (1H, br. s, N<u>H</u>), 3.78 (1H, m, C**5**-<u>H</u>), 2.11 (2H, d, *J* = 7.0 Hz, C**3**-<u>H_2</u>), 1.90 (2H, m, 2 × C**6**-<u>H_2</u>), 1.68 (2H, m, 2 × C**7**-<u>H_2</u>), 1.59 (1H, m, C**8**-<u>H_2</u>), 1.37 (2H, m, 2 × C**7**-<u>H_2</u>), 1.21–1.08 (3H, m, 2 × C**6**-<u>H_2</u>, C**8**-<u>H_2</u>), 0.91 (1H, m, C**2**-<u>H</u>), 0.58 (2H, m, 2 × C**1**-<u>H_2</u>), 0.17 (2H, m, C**1**-<u>H_2</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6 (C**4**), 48.0 (C**5**), 41.8 (C**3**), 33.3 (C**6**), 25.7 (C**8**), 24.9 (C**7**), 7.3 (C**2**), 4.7 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{11}H_{20}NO$: 182.1539. Found $[M + H]^+$: 182.1533.

1-Cyclohexylazepane-2,7-dione (330c) ***and*** **1-Cyclohexyl-3,6-dihydro-1*H*-azepine-2,7-dione (331c)**

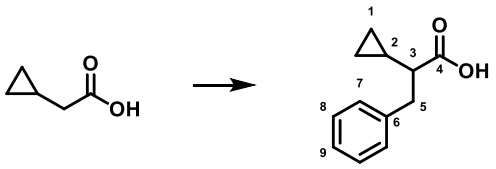


328c **330c** **331c**

General procedure B: $[Rh(cod)_2]BARF$ (13.3 mg, 0.0113 mmol), $P(C_6F_5)_3$ (12.0 mg, 0.0225 mmol), **328c** (27.2 mg, 0.150 mmol) and pyridine (0.015 mL, 0.5 M stock solution in 1,2-DCB) were employed in 1,2-DCB (2.0 mL) at 130 °C for 46 h. Purification by FCC (20% EtOAc/hexane) provided the title compounds (7.9 mg, 23%, 2:1 A:B) as a pale yellow oil; **Data for the mixture of compounds 330c and 331c**: ν_{max} / cm^{-1}: 2928 (m), 2854 (m), 17100 (m), 1661 (s), 1338 (m), 1320 (m), 1142 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.00 (2H, m, 2 × C**3**-<u>H</u>, B), 4.47–4.33 (2H, m, 2 × C**4**-<u>H</u>, A+B), 3.46 (4H, m, 4 × C**2**-<u>H_2</u>, B), 2.67 (4H, t, *J* = 6.5 Hz, 4 × C**2**-<u>H_2</u>, A), 2.18–2.03 (4H, m, 4 × C**5**-<u>H_2</u>, A+B), 1.82 (4H, t, *J* = 6.5 Hz, 4 × C**3**-<u>H_2</u>, A), 1.78–1.74 (4H, m, 4 × C**6**-<u>H_2</u>, A+B), 1.62–1.57 (2H, m, 2 × C**7**-<u>H_2</u>, A+B), 1.55–1.52 (4H, m, 4 × C**5**-<u>H_2</u>, A+B), 1.35–1.23 (4H, m, 4 × C**6**-<u>H_2</u>, A+B), 1.21–1.12 (2H, m, 2 × C**7**-<u>H_2</u>, A+B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.6 (C**1**, A), 171.6 (C**1**, B), 126.3 (C**3**, B), 56.5 (C**4**,

B), 56.4 (C**4**, A), 39.7 (C**2**, B), 37.0 (C**2**, A), 29.9 (C**5**, A), 29.4 (C**5**, B), 26.7 (C**6**, B), 26.6 (C**6**, A), 25.5 (C**7**, B), 25.5 (C**7**, A), 21.0 (C**3**, A); HRMS: (ESI$^+$) Calculated for $C_{12}H_{20}NO_2$: 210.1489. Found $[M + H]^+$: 210.1495.

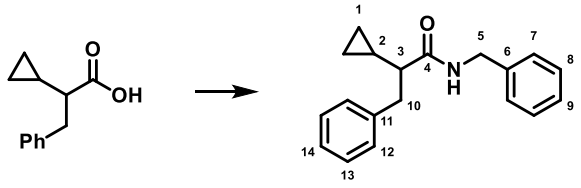
2-Cyclopropyl-3-phenylpropanoic acid (332)



327 **332**

To a flame-dried flask containing diisopropylamine (1.41 mL, 10.0 mmol) and THF (7 mL) under an atmosphere of argon at 0 °C was added *n*-BuLi (6.25 mL, 10.0 mmol, 1.6 M in THF) over 2 minutes before being stirred for 30 minutes. The resulting solution of LDA was transferred to a flask containing carboxylic acid **327** in THF (26 mL) at -78 °C over 10 minutes. After 20 minutes the reaction was warmed to 0 °C for 10 minutes and then 35 °C for 10 minutes. The reaction was then cooled to room temperature before the addition of benzyl chloride (575 mg, 5.00 mmol). After 30 minutes the reaction was quenched by the addition of water (20 mL). The organic phase was removed and the aqueous layer was washed with Et_2O (20 mL). The aqueous layer was acidified by the addition of 1 M HCl (5 mL) before being extracted with Et_2O (3 × 20 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by FCC (10% EtOAc/hexane) provided the title compound (780 mg, 82%) as a colourless oil; ν_{max} / cm^{-1}: 2923 (m), 1704 (s), 1290 (w), 1229 (w); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.22 (1H, br. s, O<u>H</u>), 7.34–7.24 (5H, m, 2 × C**7**-<u>H</u>, 2 × C**8**-<u>H</u>, C**9**-<u>H</u>), 3.15 (1H, dd, *J* = 13.5, 8.5 Hz, C**5**-<u>H</u>$_2$), 3.01 (1H, dd, *J* = 13.5, 6.0 Hz, C**5**-<u>H</u>$_2$), 1.95 (1H, m, C**3**-<u>H</u>), 1.05 (1H, m, C**2**-<u>H</u>), 0.60–0.58 (2H, m, 2 × C**1**-<u>H</u>$_2$), 0.41 (1H, m, C**1**-<u>H</u>$_2$), 0.12 (1H, m, C**1**-<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 181.2 (C**4**), 139.2 (C**6**), 129.1, 128.5 (C**7**, C**8**), 126.5 (C**9**), 52.6 (C**3**), 38.5 (C**5**), 13.8 (C**2**), 5.0 (C**1**), 3.8 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{12}H_{14}NaO_2$: 213.0886. Found $[M + Na]^+$: 213.0886.

***N*-Benzyl-2-cyclopropyl-3-phenylpropanamide (333a)**

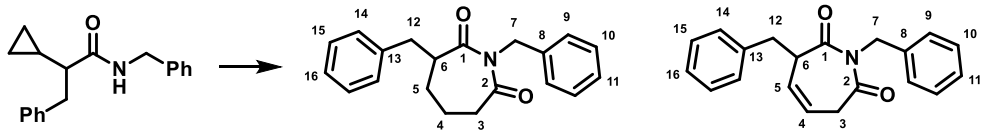


332 **333a**

To a stirring solution of carboxylic acid **332** (700 g, 3.68 mmol), DCC (836 mg, 4.05 mmol) and DMAP (spatula tip) in dry CH_2Cl_2 (12 mL) at 0 °C was added benzylamine (0.42 mL, 3.86 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h before being filtered over a short pad of celite. The filtrate was concentrated *in vacuo* and purified by FCC (15–20% EtOAc/hexane) to provide

the title compound (261 mg, 26%) as a colourless solid; m.p. 111–113 °C (CH_2Cl_2/hexane); ν_{max} / cm^{-1}: 3295 (m), 1637 (s), 1541 (s), 1452 (m), 1220 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.24 (8H, m, 8 × ArC<u>H</u>), 7.10–7.08 (2H, m, 2 × ArC<u>H</u>), 5.76 (1H, br. m, N<u>H</u>), 4.48 (1H, dd, *J* = 15.0, 6.0 Hz, C**5**-<u>H</u>$_2$), 4.49 (1H, dd, *J* = 15.0, 5.5 Hz, C**5**-<u>H</u>$_2$), 3.19 (1H, dd, *J* = 13.5, 9.0 Hz, C**10**-<u>H</u>$_2$), 3.07 (1H, dd, *J* = 13.5, 5.0 Hz, C**10**-<u>H</u>$_2$), 1.67 (1H, m, C**3**-<u>H</u>), 1.09 (1H, m, C**2**-<u>H</u>), 0.64 (2H, m, 2 × C**1**-<u>H</u>$_2$), 0.30 (1H, m, C**1**-<u>H</u>$_2$), 0.18 (1H, m, C**1**-<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.2 (C**4**), 139.9 (C**11**), 138.3 (C**6**), 129.4, 128.7, 128.5, 127.7 (C**7**, C**8**, C**12**, C**13**), 127.4, 126.3 (C**9**, C**14**), 55.2 (C**3**), 43.5 (C**5**), 38.9 (C**10**), 13.7 (C**2**), 5.0 (C**1**), 4.4 (C**1**); HRMS: (ESI$^+$) Calculated for $C_{19}H_{22}NO$: 280.1696. Found [M + H]$^+$: 280.1698.

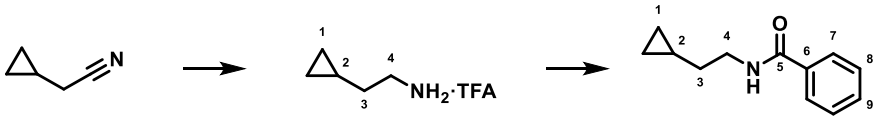
1,3-Dibenzylazepane-2,7-dione (335a) *and* 1,3-Dibenzyl-3,6-dihydro-1*H*-azepine-2,7-dione (336a)



333a **335a** **336a**

General procedure B: [Rh(cod)$_2$]BARF (13.3 mg, 0.0113 mmol), P(C_6F_5)$_3$ (12.0 mg, 0.0225 mmol), amide **333a** (41.9 mg, 0.150 mmol) and pyridine (0.015 mL, 0.5 M stock solution in 1,2-DCB) were employed in 1,2-DCB (2.0 mL) at 130 °C for 46 h. ^{1}H NMR analysis of the crude reaction against 1,4-DNB as an internal standard suggests **335a** and **336a** (45%, 1.8:1 mixture of **69**:**70**). Analytical samples of **335a** and **336a** were obtained in an impure form by FCC (15% EtOAc/hexane); **Data for the saturated product 335a**: ν_{max} / cm^{-1}: 2936 (w), 1661 (s), 1341 (m), 1330 (m), 1168 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27–7.12 (10H, m, 2 × C**9**-<u>H</u>, 2 × C**10**-<u>H</u>, C**11**-<u>H</u>, 2 × C**14**-<u>H</u>, 2 × C**15**-<u>H</u>, C**16**-<u>H</u>), 5.00 (1H, d, *J* = 14.0 Hz, C**7**-<u>H</u>$_2$), 4.89 (1H, d, *J* = 14.0 Hz, C**7**-<u>H</u>$_2$), 3.27 (1H, dd, *J* = 14.0, 7.0 Hz, C**12**-<u>H</u>$_2$), 2.99 (1H, m, C**6**-<u>H</u>), 2.84 (1H, dd, *J* = 18.0, 5.0 Hz, C**3**-<u>H</u>$_2$), 2.72 (1H, dd, *J* = 14.0, 7.0 Hz, C**12**-<u>H</u>$_2$), 2.64 (1H, m, C**3**-<u>H</u>$_2$), 1.91–1.66 (4H, m, C**4**-<u>H</u>$_2$, C**5**-<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.9, 176.9 (C**1**, C**2**), 139.4 (C**13**), 137.8 (C**8**), 129.2, 128.6, 128.5, 128.3 (C**9**, C**10**, C**14**, C**15**), 127.3, 126.5 (C**11**, C**16**), 47.1 (C**7**), 46.9 (C**6**), 37.6 (C**12**), 37.0 (C**3**), 28.8 (C**5**), 20.1 (C**4**); HRMS: (ESI$^+$) Calculated for $C_{20}H_{21}NNaO_2$: 330.1465. Found [M + Na]$^+$: 330.1455. **Data for the unsaturated product 336a**: ν_{max} / cm^{-1}: 2925 (w), 1710 (m), 1662 (s), 1454 (m), 1305 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.18 (10H, m, ArC<u>H</u>), 5.94 (1H, m, C**4**-<u>H</u>), 5.81 (1H, m, C**5**-<u>H</u>), 5.04 (1H, d, *J* = 14.5 Hz, C**7**-<u>H</u>$_2$), 4.96 (1H, d, *J* = 14.5 Hz, C**7**-<u>H</u>$_2$), 3.89 (1H, m, C**6**-<u>H</u>), 3.66 (1H, m, C**3**-<u>H</u>$_2$), 3.50 (1H, dd, *J* = 17.0, 7.5 Hz, C**3**-<u>H</u>$_2$), 3.44 (1H, dd, *J* = 14.5, 6.0 Hz, C**12**-<u>H</u>$_2$), 3.00 (1H, dd, *J* = 14.5, 9.0 Hz, C**12**-<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.1 (C**1**), 171.0 (C**2**), 138.8 (C**13**), 137.8 (C**8**), 132.1 (C**5**), 129.2, 128.7, 128.4, 128.3, 127.3, 126.7 (C**9**, C**10**, C**11**, C**14**, C**15**, C**16**), 125.1 (C**4**), 48.2 (C**6**), 46.0 (C**7**), 39.8 (C**3**), 35.7 (C**12**); HRMS: (ESI$^+$) Calculated for $C_{20}H_{19}NNaO_2$: 328.1308. Found [M + Na]$^+$: 328.1320.

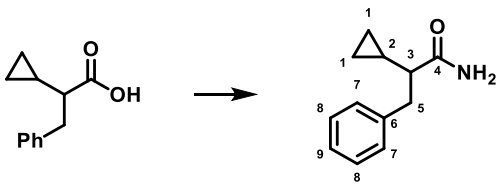
***N*-(2-Cyclopropylethyl)benzamide (338)**



326 **338**

$LiAlH_4$ powder (569 mg, 15.0 mmol) was added to a flask which was sealed with a rubber septum and purged with argon for 20 minutes. The flask was cooled to 0 °C before adding conc. H_2SO_4 (0.41 mL, 7.50 mmol) dropwise over 15 minutes (gas evolved). The flask was warmed to room temperature and stirred for 1 h. To the resulting grey suspension was added cyclopropylacetonitrile **326** (0.46 mL, 5.00 mmol) in THF (5 mL) over 10 minutes. The reaction mixture was warmed to 40 °C for 2 h and then cooled to 0 °C, diluted with Et_2O (20 mL) and quenched by the dropwise addition of water (20 mL) over 2 minutes. KOH pellets (~1 g) were added and the mixture was stirred for 15 minutes causing the grey suspension to separate into a colourless aqueous suspension and a clear colourless organic layer. The organic phase was separated and the aqueous was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over $MgSO_4$ and filtered. trifluoroacetic acid (3.5 mL) was added to the organic phase allowing the intermediate amine to be isolated as a brown liquid trifluoroacetic acid salt (1.81 g) after being concentrated *in vacuo*. Half of the amine salt (0.90 g, assumed ~2.50 mmol) was added to solution of NaOH (250 mg, 6.25 mmol) in water (63 mL, 0.04 M). Benzoyl chloride (0.32 mL, 2.75 mmol) was then added to the solution causing the formation of a colourless solid. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phase was dried over $MgSO_4$ before being concentrated *in vacuo*. The resulting crude product was purified by FCC (25% EtOAc/hexane) to provide the title compound (340 mg, 72% over 2 steps on a 2.50 mmol scale) as a colourless solid; m.p. 56–57 °C (CH_2Cl_2); ν_{max} / cm^{-1}: 3302 (br.), 3075 (w), 3000 (w), 2925 (w), 1635 (s), 1539 (s), 1490 (m), 1310 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77–7.75 (2H, m, C**7**-H), 7.47 (1H, m, C**9**-H), 7.42 (2H, m, C**8**-H), 6.29 (1H, br. s, NH), 3.55 (2H, td, *J* = 7.0, 6.5 Hz, C**4**-H_2), 1.53 (2H, dt, *J* = 7.0, 7.0 Hz, C**3**-H_2), 0.74 (1H, m, C**2**-H), 0.50 (2H, m, C**1**-H), 0.12 (2H, m, C**1**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5 (C**5**), 135.0 (C**6**), 131.4 (C**9**), 128.7 (C**8**), 126.9 (C**7**), 40.5 (C**4**), 34.6 (C**3**), 8.8 (C**2**), 4.3 (C**1**); HRMS: (ESI^+) Calculated for $C_{12}H_{16}NO$: 190.1226. Found $[M + H]^+$: 190.1235.

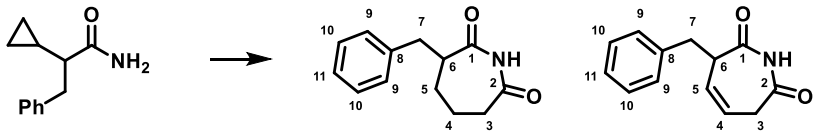
2-Cyclopropyl-3-phenylpropanamide (333b)



332 **333b**

To a stirring solution of carboxylic acid **332** (3.80 g, 20.0 mmol) in dry CH_2Cl_2 (20 mL), at 0 °C was added a drop of DMF and then oxalyl chloride (1.88 mL, 22.0 mmol) over 5 minutes. The resulting solution was stirred for 30 minutes before being added to a stirring solution of aq. ammonia (40 mL) resulting in immediate formation of a colourless precipitate. After 30 minutes the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by FCC (50% EtOAc/hexane) to provide the title compound (2.87 g, 76%) as a colourless solid; m.p. 107–108 °C (CH_2Cl_2); ν_{max} / cm^{-1} 3398 (s), 3189 (m), 1653 (s), 1621 (s), 1409 (m), 1284 (w); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.21 (5H, m, 2 × C**7**-H, 2 × C**8**-H, 1 × C**9**-H), 5.79 (1H, br. s, 1 × NH), 5.59 (1H, br. s, 1 × NH), 3.14 (1H, dd, *J* = 13.5, 8.0 Hz, 1 × C**5**-H_2), 3.02 (1H, dd, *J* = 13.5, 5.5 Hz, 1 × C**5**-H_2), 1.71 (1H, m, C**3**-H), 0.63–0.60 (2H, m, 2 × C**1**-H_2), 0.31 (1H, m, 1 × C**1**-H_2), 0.13 (1H, m, 1 × C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.2 (C**4**), 139.8 (C**6**), 129.3, 128.4 (C**7**, C**8**), 126.3 (C**9**), 54.0 (C**3**), 38.9 (C**5**), 13.6 (C**2**), 5.1 (C**1**), 4.3 (C**1**); HRMS: (ESI^+) Calculated for $C_{12}H_{15}NNaO$: 212.1046. Found $[M + Na]^+$: 212.1052.

3-Benzylazepane-2,7-dione (335b) *and* 3-Benzyl-3,6-dihydro-1*H*-azepine-2,7-dione *and* 6-Benzyl-3,4-dihydro-1*H*-azepine-2,7-dione (336b)

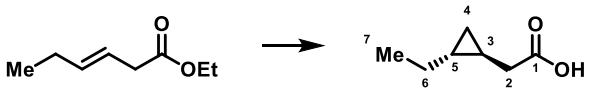


333b **335b** **336b**

General procedure B: $[Rh(cod)_2]BARF$ (8.9 mg, 0.0075 mmol), $P(C_6F_5)_3$ (8.0 mg, 0.015 mmol), amide **333b** (28.4 mg, 0.150 mmol) and pyridine (0.015 mL, 0.5 M stock solution in 1,2-DCB) were employed in 1,2-DCB (2.0 mL) at 130 °C for 46 h. ^{1}H NMR analysis of the crude reaction against 1,4-DNB as an internal standard suggests **335b** and **336b** (79%, 2:1 mixture of **335b**:**336b**). Analytical samples of **335b** and **336b** were obtained in an impure form by FCC (15% EtOAc/hexane); **Data for the saturated product 335b**: ν_{max} / cm^{-1} 3228 (br.), 2923 (w), 1696 (s), 1271 (m), 1198 (w); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, br. s, NH), 7.31–7.19 (5H, m, 2 × C**9**-H, 2 × C**10**-H, 1 × C**11**-H), 3.30 (1H, dd, *J* = 14.0, 5.5 Hz, 1 × C**7**-H_2), 2.97 (1H, m, C**6**-H), 2.76–2.61 (3H, m, 2 × C**3**-H_2, 1 × C**7**-H_2), 1.95–1.79 (3H, m, 2 × C**4**-H_2, 1 × C**5**-H_2), 1.69 (1H, m, 1 × C**5**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.6 (C**1**), 175.2 (C**2**), 139.1 (C**8**), 129.2, 128.6 (C**9**, C**10**), 126.6 (C**11**), 45.0 (C**6**), 36.9 (C**7**), 35.1 (C**3**), 27.5 (C**5**), 20.0 (C**4**); HRMS: (ESI^+) Calculated for $C_{13}H_{15}NNaO_2$: 240.0995. Found $[M + Na]^+$: 240.0997. **Data for the unsaturated product 336b**: ν_{max} / cm^{-1} 3217 (br.), 2935 (w), 1684 (s), 1353 (m), 1260 (m), 1203 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (1H, br. s, NH), 7.31 (2H, m, 2 × C**10**-H), 7.26–7.21 (3H, m, 2 × C**9**-H, C**11**-H), 5.93 (1H, m, C**4**-H), 5.78 (1H, m, C**5**-H), 3.78 (1H, m, C**6**-H), 3.51 (1H, m, 1 × C**3**-H_2), 3.44 (1H, dd, *J* = 14.5, 5.5 Hz, 1 × C**7**-H_2), 3.35 (1H, dd, *J* = 16.5, 8.0 Hz, 1 × C**3**-H_2), 2.96 (1H, dd, *J* = 14.5, 9.0 Hz, 1 × C**7**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5 (C**1**), 170.5

(C**2**), 138.5 (C**8**), 131.6 (C**5**), 129.2 (C**9**), 128.8 (C**10**), 126.6 (C**11**), 124.6 (C**4**), 47.0 (C**6**), 37.8 (C**3**), 34.9 (C**7**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{13}NNaO_2$: 238.0838. Found $[M + Na]^+$: 238.0845.

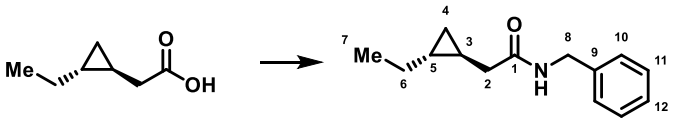
2-((1*S,2*R**)-2-Ethylcyclopropyl)acetic acid (342)**



342

Ethyl ester **I** (0.80 mL, 5.00 mmol) and CH_2I_2 (2.42 mL, 30.0 mmol) were added by syringe to a flame-dried flask containing dry CH_2Cl_2 (20 mL). The flask was cooled to -10 °C. Et_2Zn (15 mL, 15.0 mmol, 1 M Hex) was then added by syringe over 5 minutes and the resulting mixture was stirred for 2 h. Sat. aq. EDTA (10 mL) was added and the resulting mixture was filtered through celite. The organic layer was separated, washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture showed complete consumption of the starting material. 0.5 M aq. NaOH (20 mL) was added and the mixture was heated at reflux for 1 h. Once cooled, the aqueous layer was washed with Et_2O (20 mL), acidified with conc. HCl and extracted with Et_2O (3 × 20 mL). The product containing organics were dried over Mg_2SO_4, filtered and concentrated *in vacuo* to provide the title compound (499 mg, 78%, single diastereomer) as a pale yellow oil; ν_{max} / cm^{-1} 2922 (s), 2851 (m), 1707 (s), 1458 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.27 (2H, dd, *J* = 7.0, 2.0 Hz, C**2**-$\underline{H}_2$), 1.26 (2H, m, C**6**-$\underline{H}_2$), 0.95 (2H, t, *J* = 7.5 Hz, C**7**-$\underline{H}_3$), 0.79 (1H, m, C**3**-$\underline{H}$), 0.54 (1H, m, C**5**-$\underline{H}$), 0.33 (2H, m, C**4**-$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.7 (C**1**), 39.0 (C**2**), 27.0 (C**6**), 20.6 (C**5**), 13.9 (C**3**), 13.6 (C**7**), 11.5 (C**4**); HRMS: **342** was not observed by +ESI or -ESI.

***N*-Benzyl-2-((1*S**,2*R**)-2-ethylcyclopropyl)acetamide (343a)**

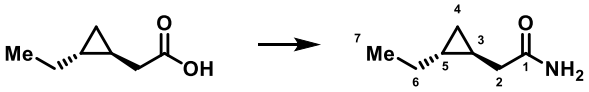


342 **343a**

To a flame dried flask containing EDCI (449 mg, 2.34 mmol) and DMAP (24 mg, 0.20 mmol) under an atmosphere of argon was added CH_2Cl_2 (10 mL) and benzylamine (0.43 mL, 3.90 mmol). The flask was cooled to 0 °C before the addition of carboxylic acid **342** (250 mg, 1.95 mmol). The reaction mixture was stirred for 24 h before being concentrated *in vacuo*. The resulting solid dissolved in 1 M aq. NaOH (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organics were washed with 1 M aq. HCl (10 mL), dried over $MgSO_4$ before being concentrated *in vacuo*. Purification by FCC (25% EtOAc/hexane) provided the title compound (161 mg, 38%) as a colourless solid; m.p. 41–42 °C (CH_2Cl_2); ν_{max} / cm^{-1} 3293 (m), 2961 (m), 1631 (s), 1549 (s), 1453 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.28 (5H, m, C**10**-$\underline{H}$, C**11**-$\underline{H}$, C**12**-$\underline{H}$), 6.13 (1H, br. s, N$\underline{H}$), 4.47 (2H, d, *J* = 5.5 Hz, C**8**-$\underline{H}_2$), 2.26

(1H, dd, *J* = 16.0, 7.0 Hz, C**2**-$\underline{H}_2$), 2.15 (1H, dd, *J* = 16.0, 7.5 Hz, C**2**-$\underline{H}_2$), 1.24 (2H, m, C**6**-$\underline{H}_2$), 0.92 (3H, t, *J* = 7.5 Hz, C**7**-$\underline{H}_3$), 0.70 (1H, m, C**3**-$\underline{H}$), 0.56 (1H, m, C**5**-$\underline{H}$), 0.35 (2H, m, C**4**-$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6 (C**1**), 138.5 (C**9**), 128.8, 127.8 (C**10**, C**11**), 127.6 (C**12**), 43.6 (C**8**), 41.3 (C**2**), 26.9 (C**6**), 20.8 (C**3**), 14.5 (C**5**), 13.7 (C**7**), 11.8 (C**4**); HRMS: (ESI^+) Calculated for $C_{14}H_{20}NO$: 218.1539. Found $[M + H]^+$: 218.1536.

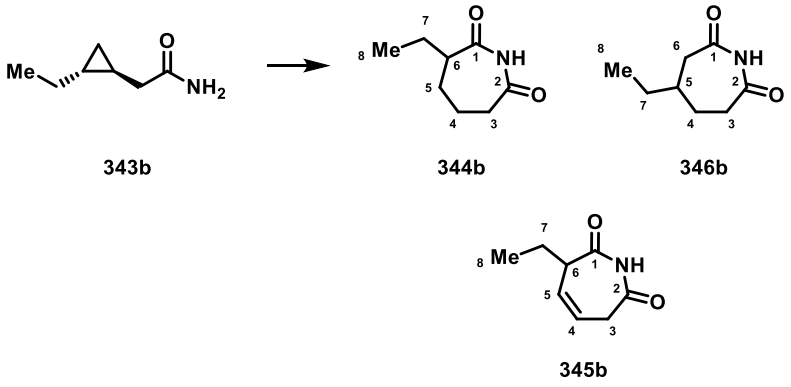
2-((1*S,2*R**)-2-Ethylcyclopropyl)acetamide (343b)**



342 **343b**

To a stirring solution of carboxylic acid **342** (250 mg, 1.95 mmol) in dry CH_2Cl_2 (2 mL), at 0 °C was added a drop of DMF and then oxalyl chloride (0.19 mL, 2.15 mmol) over 5 minutes. The resulting solution was stirred for 30 minutes before being added to a stirring solution of aq. ammonia (5 mL) resulting in immediate formation of a colourless precipitate. After 30 minutes the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by FCC (70% EtOAc/hexane) to provide the title compound (170 mg, 69%) as a colourless solid; m.p. 86–89 °C (CH_2Cl_2); ν_{max} / cm^{-1} 3349 (br. m), 3175 (br. m), 2960 (m), 1660 (s), 1630 (s), 1415 (s), 1278 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.80 (2H, br. m, N$\underline{H}_2$), 2.24 (1H, dd, *J* = 16.0, 7.0 Hz, C**2**-$\underline{H}_2$), 2.11 (1H, dd, *J* = 16.0, 7.5 Hz, C**2**-$\underline{H}_2$), 1.27 (2H, m, C**6**-$\underline{H}_2$), 0.96 (3H, t, *J* = 7.5 Hz, C**7**-$\underline{H}_3$), 0.71 (1H, m, C**3**-$\underline{H}$), 0.57 (1H, m, C**5**-$\underline{H}$), 0.36 (2H, m, C**4**-$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.6 (C**1**), 40.9 (C**2**), 27.0 (C**6**), 20.8 (C**3**), 14.6 (C**5**), 13.7 (C**7**), 11.8 (C**4**); HRMS: (ESI^+) Calculated for $C_7H_{13}NO$: 128.1070. Found $[M + H]^+$: 128.1070k.

3-Ethylazepane-2,7-dione (344b), 3-Ethyl-3,6-dihydro-1H-azepine-2,7-dione (345b) *and* 4-Ethylazepane-2,7-dione (346b)



343b **344b** **346b**

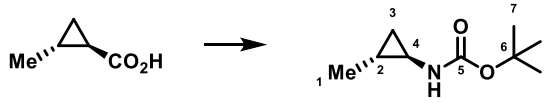
345b

General procedure B: $[Rh(cod)_2]BARF$ (8.87 mg, 0.0075 mmol), $P(C_6F_5)_3$ (8.0 mg, 0.015 mmol), amide **343b** (19.1 mg, 0.150 mmol) and pyridine (0.015 mL, 0.5 M stock solution in 1,2-DCB) were employed in 1,2-DCB (2.0 mL) at 130 °C for 46 h. ^{1}H NMR analysis of the crude reaction against 1,4-

DNB as an internal standard suggests a 43% yield (5:1:1 mixture of **344b**:**345b:346b**). Analytical samples of **344b** and **345b** were obtained in an impure form by FCC (15% EtOAc/hexane); **Data for the saturated (C6-substituted) 344b:** ν_{max} / cm^{-1} 3183 (br. w), 1698 (s), 1669 (s), 1363 (s), 1208 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (1H, br. s, NH), 2.82–2.67 (2H, m, 2 × C**3**-H_2), 2.61 (1H, m, C**6**-H), 2.05–1.90 (4H, m, 2 × C**4**-H_2, 1 × C5-H_2, 1 × C**7**-H_2), 1.69 (1H, m, 1 × C**5**-H_2), 1.50 (1H, m, 1 × C**7**-H_2), 0.98 (3H, t, J = 7.5 Hz, C**8**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.8 (C**1**), 175.1 (C**2**), 44.8 (C**6**), 35.2 (C**3**), 27.9 (C**5**), 24.1 (C**7**), 20.2 (C**4**), 12.0 (C**8**); HRMS: ($APCI^+$) Calculated for $C_8H_{13}NO_2$: 156.1019. Found $[M + H]^+$: 156.1019. **Data for the unsaturated (C6-substituted) 345b:** ν_{max} / cm^{-1} 3223 (br. w), 1690 (s), 1276 (m), 1201 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (1H, br. s, NH), 5.99 (1H, m, C**4**-H), 5.74 (1H, m, C**5**-H), 3.55 (1H, m, 1 × C**3**-H_2), 3.41–3.31 (2H, m, 1 × C**3**-H_2, 1 × C**6**-H), 2.07 (1H, m, 1 × C**7**-H_2), 1.71 (1H, m, 1 × C**7**-H_2), 1.02 (3H, t, *J* = 7.5 Hz, C**8**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.8 (C**1**), 170.7 (C**2**), 132.2 (C**5**), 124.4 (C**4**), 47.2 (C**6**), 37.9 (C**3**), 22.2 (C**7**), 11.7 (C**8**); HRMS: ($APCI^+$) Calculated for $C_8H_{11}NO_2$: 154.0863. Found $[M + H]^+$: 154.0865. **Data for the saturated (C5-substituted) 346b:** ν_{max} / cm^{-1} 3334 (br. w), 3185 (br. w), 1666 (s), 1695 (s), 1460 (w), 1203 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, br. s, NH), 2.79–2.69 (3H, m, 2 × C**3**-H_2, 1 × C**6**-H_2), 2.58 (1H, dd, *J* = 14.5, 8.0 Hz, 1 × C**6**-H_2), 2.10 (1H, m, 1 × C**4**-H_2), 1.96 (1H, m, C**5**-H), 1.55 (1H, m, 1 × C**4**-H_2), 1.40 (2H, m, 2 × C**7**-H_2), 0.94 (3H, t, *J* = 7.5 Hz, C**8**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.1 (C**2**), 173.7 (C**1**), 40.3 (C**6**), 34.2 (C**5**), 34.2 (C**3**), 29.2 (C**7**), 27.0 (C**4**), 11.5 (C**8**); HRMS: ($APCI^+$) Calculated for $C_8H_{13}NO_2$: 156.1019. Found $[M + H]^+$: 156.1021.

4.4 Experimental procedures for the studies in Section 3.2

tert-Butyl ((1*R**,2*R**)-2-methylcyclopropyl)carbamate (*trans*-213a)



***trans*-212a** **trans-213a**

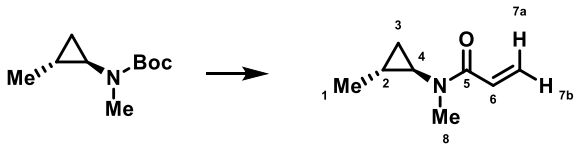
General Procedure D: Carboxylic acid ***trans*-212a** (10.0 g, 100 mmol) was employed and the reaction was heated for 72 h. FCC (5% EtOAc/hexane) provided the title compound (15.0 g, 88%, 8:1 d.r. A:B) as a colourless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.68 (2H, br. s, NH, A+B), 2.53 (1H, m, C**4**-H, B), 2.19 (1H, m, C**4**-H, A), 1.40 (18H, s, C**7**-H_3, A+B), 1.07–1.05 (6H, m, C**1**-H_3, A+B), 0.96–0.78 (3H, m, 2 × C**2**-H (A+B), 1 × C**3**-H_2, A), 0.60 (1H, m, C**3**-H_2, A), 0.44 (C**3**-H_2, A), 0.05 (1H, m, C**3**-H_2, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.0 (C**5**, A), 79.4 (C**6**, A+B), 30.4 (C**4**, A), 28.5 (C**7**, A), 28.5 (C**7**, B), 17.3 (C**1**, A), 15.2 (C**2**, A), 15.0 (C**3**, A), 12.4 (C**1**, B). *The spectroscopic properties of this compound were consistent with the data available in the literature*[99]

tert-Butyl methyl((1*R**,2*R**)-2-methylcyclopropyl)carbamate (401)

***trans*-213a** **401**

General Procedure G: Carbamate ***trans*-213a** (3.42 g, 20.0 mmol) was employed in THF (67 mL) using NaH (1.20 g, 30.0 mmol) and MeI (3.74 mL, 60.0 mmol). The reaction was run for 16 h at room temperature. FCC (3% EtOAc/hexane) provided the title compound (2.54 g, 69%, 8:1 d.r., A:B) as a pale yellow oil; ν_{max} / cm^{-1}: 2973 (m), 1697 (s), 1364 (s), 1153 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.83 (3H, s, C**10**-H_3, B), 2.79 (3H, s, C**8**-H_3, A), 2.55 (1H, m, C**4**-H, B), 2.12 (1H, m, C**4**-H, A), 1.46 (18H, s, C**7**-H_3, A+B), 1.05 (3H, d, *J* = 6.0 Hz, C**1**-H_3, A), 1.02 (3H, d, *J* = 5.5 Hz, C**1**-H_3, B), 0.99–0.89 (2H, m, 2 × C**2**-H, A+B), 0.82 (1H, m, C**3**-H_2, B), 0.69 (1H, m, C**3**-H_2, A), 0.43 (1H, m, C**3**-H_2, A), 0.22 (1H, m, C**3**-H_2, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.0 (C**5**), 79.1 (C**6**), 37.9 (C**4**), 28.5 (C**7**), 28.4 (C**1**), 17.2 (C**2**), 15.3 (C**3**); HRMS: (ESI^+) Calculated for $C_{10}H_{19}NNaO_2$: 208.1308. Found $[M + H]^+$: 208.1317.

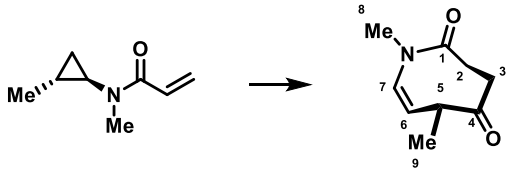
N-Methyl-*N*-((1*R**,2*R**)-2-methylcyclopropyl)acrylamide (402)



***trans*-213a** **402**

General Procedure H: Carbamate **401** (7.20 g, 38.9 mmol) was employed. FCC (20% EtOAc/hexane) provided the title compound (4.89 g, 90%, 8:1 d.r.) as a pale yellow oil; ν_{max} / cm^{-1}: 3485 (br.), 2956 (m), 1653 (s), 1615 (s), 1428 (m), 1402 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.82 (1H, dd, *J* = 17.0, 10.5 Hz, C**6**-H), 6.31 (1H, dd, *J* = 17.0, 2.0 Hz, C**7a**-H), 5.64 (1H, dd, *J* = 10.5, 2.0 Hz, C**7b**-H), 2.94 (3H, s, C**8**-H_3), 2.37 (1H, m, C**4**-H), 1.11 (3H, d, *J* = 5.5 Hz, C**1**-H_3), 1.09–1.00 (1H, m, C**2**-H), 0.85 (1H, m, C**3**-H_2), 0.63 (1H, m, C**3**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1 (C**5**), 129.0 (C**6**), 127.1 (C**7**), 38.5 (C**4**), 34.2 (C**8**), 17.5 (C**2**), 17.0 (C**1**), 16.7 (C**3**); HRMS: (ESI^+) Calculated for $C_8H_{14}NO$: 140.1070. Found $[M + H]^+$: 140.1058.

(*Z*)-1,6-Dimethyl-1,3,4,6-tetrahydroazocine-2,5-dione (403a)

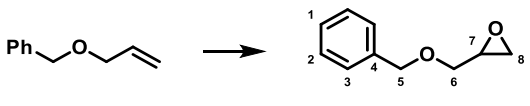


402 **403a**

General Procedure I: (*Screening conditions for optimum yield*) Acrylamide **402** (20.3 mg, 0.150 mmol), $[Rh(cod)_2]BARF$ (17.7 mg, 0.0150 mmol), $P(p\text{-}CNC_6H_4)_3$ (12.7 mg, 0.0375 mmol) and *N*-methyltrifluoroacetamide (19.1 mg, 0.150 mmol) were employed, and the reaction was heated at 150 °C for 72 h. ^{1}H NMR analysis of the crude reaction mixture against 1,4-DNB as an internal standard indicated formation of the title compound (51% yield).

General Procedure I: (*Multi-mmol scale reaction for material throughput*) Acrylamide **402** (696 mg, 5.00 mmol), $[Rh(cod)_2]BARF$ (296 mg, 0.250 mmol), $P(p\text{-}CNC_6H_4)_3$ (169 mg, 0.500 mmol) and *N*-methyltrifluoroacetamide (317 mg, 2.50 mmol) were employed and the reaction was heated at 150 °C for 72 h. FCC (50% EtOAc/hexane) was followed by further FCC (50% Et_2O/hexane) to provide the title compound (406 mg, 49%) as a pale yellow oil which solidified on standing; m.p. 35–38 °C ($CHCl_3$); ν_{max} / cm^{-1}: 2942 (w), 1705 (m), 1652 (s), 1640 (s), 1449 (m), 1382 (m), 1028 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.15 (1H, dd, *J* = 7.5, 1.0 Hz, C**7**-H), 5.16 (1H, dd, *J* = 9.0, 7.5 Hz, C**6**-H), 3.49 (1H, m, C**5**-H), 3.07 (3H, s, C**8**-H_3), 2.86–2.61 (2H, m, 1 × C**2**-H_2, 1 × C**3**-H_2), 2.56–2.43 (2H, m, 1 × C**2**-H_2, 1 × C**3**-H_2), 1.15 (3H, d, *J* = 6.5 Hz, C**9**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.6 (C**4**), 173.0 (C**1**), 131.9 (C**7**), 125.9 (C**6**), 43.8 (C**5**), 38.9 (C**3**), 34.1 (C**8**), 32.6 (C**2**), 15.2 (C**9**); HRMS: (ESI^+) Calculated for $C_9H_{14}NO_2$: 168.1019. Found $[M + H]^+$: 168.1017.

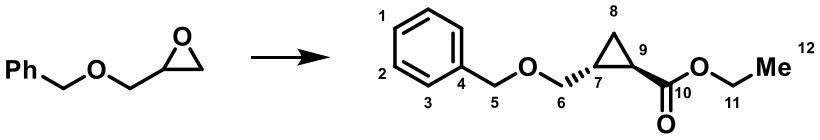
2-((Benzyloxy)methyl)oxirane (404)



404

To a stirring solution of allyl ether **I** (12.6 g, 85.0 mmol) at 0 °C in CH_2Cl_2 (260 mL), was added *m*-CPBA (22.4 g, 130 mmol) in one portion. The resulting suspension was stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (250 mL), washed with sat. aq. Na_2SO_3 (250 mL), sat. aq. $NaHCO_3$ (3 × 250 mL) and brine (250 mL) before drying over Na_2SO_4 and concentrating *in vacuo* to provide the title compound (13.1 g, 94%) as a colourless oil; ν_{max} / cm^{-1}: 2862 (w), 1453 (m), 1253 (m), 1094 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.27 (5H, m, C**1**-H, 2 × C**2**-H, 2 × C**3**-H), 4.63 (1H, d, *J* = 12.0 Hz, C**5**-H_2), 4.57 (1H, d, *J* = 12.0 Hz, C**5**-H_2), 3.77 (1H, dd *J* = 11.5, 3.0 Hz, C**6**-H_2), 3.45 (1H, dd, *J* = 11.5, 6.0 Hz, C**6**-H_2), 3.20 (1H, m, C**7**-H), 2.81 (1H, dd, *J* = 5.0, 4.5 Hz, C**8**-H_2), 2.63 (1H, dd, *J* = 5.0, 2.5 Hz, C**8**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.0 (C**4**), 128.6, 127.9 (C**1**, C**2**, C**3**), 73.5 (C**5**), 71.0 (C**6**), 51.0 (C**7**), 44.5 (C**8**); HRMS: (ESI^+) Calculated for $C_{10}H_{12}NaO_2$: 187.0730. Found $[M + Na]^+$: 187.0737.

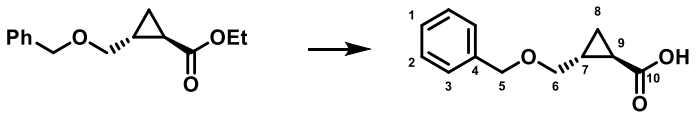
Ethyl (1*R,2*R**)-2-((benzyloxy)methyl)cyclopropane-1-carboxylate (405a)**



404 **405a**

A flame-dried, two-necked flask containing NaH (3.72 g, 93.0 mmol, 60% dispersion in mineral oil) was fitted with a reflux condenser and placed under an atmosphere of nitrogen before the addition of anhydrous 1,2-DME (70 mL). While stirring, triethyl phosphonoacetate (24.0 mL, 121 mmol) was added to the resulting suspension over 1 h using a syringe pump. The resulting solution was stirred for 1 h before the dropwise addition of epoxide **404** (11.5 g, 70.0 mmol) over 1.5 h using a syringe pump. The reaction mixture was heated at 60 °C for 2 h then at reflux for 22 h before being cooled to room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl (150 mL) and extracted with EtOAc (2 × 150 mL). The combined organics were washed with brine (150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% EtOAc/hexane) provided the title compound (8.57 g, 52%) as a pale yellow oil. *The product was assigned as the trans-diastereomer in accordance with the reported selectivity of the cyclopropanation*; ν_{max} / cm^{-1}: 2980 (w), 2863 (w), 1722 (s), 1453 (w), 1182 (s), 1092 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.27 (5H, m, C**1**-H, 2 × C**2**-H, 2 × C**3**-H), 4.52 (2H, s, C**5**-H_2), 4.12 (2H, q, *J* = 7.0 Hz, C**11**-H_2), 3.45 (1H, dd, *J* = 10.5, 6.0 Hz, C**6**-H_2), 3.37 (1H, dd, *J* = 10.5, 6.0 Hz, C**6**-H_2), 1.74 (1H, m, C**7**-H), 1.56 (1H, m, C**9**-H), 1.26 (3H, t, *J* = 7.0 Hz, C**12**-H_3), 1.21 (1H, m, C**8**-H_2), 0.86 (1H, m, C**8**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.0 (C**10**), 138.3 (C**4**), 128.6, 127.8, (C**2**, C**3**), 127.8 (C**1**), 72.8 (C**5**), 71.7 (C**6**), 60.7 (C**11**), 21.7 (C**7**), 18.7 (C**9**), 14.4 (C**12**), 13.1 (C**8**); HRMS: (ESI^+) Calculated for $C_{14}H_{18}NaO_3$: 257.1148. Found $[M + Na]^+$: 257.1151.

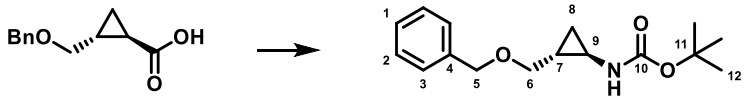
(1*R,2*R**)-2-((Benzyloxy)methyl)cyclopropane-1-carboxylic acid (406a)**



405a 406a

General Procedure C: Ester **405a** (10.5 g, 45.0 mmol) was employed and the reaction was stirred at room temperature for 16 h. The title compound (9.04 g, 97%) was isolated as a colourless oil; ν_{max} / cm^{-1}: 2861 (w), 2664 (br.), 1692 (s), 1454 (m), 1229 (m), 1081 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.27 (5H, m, C**1**-H, 2 × C**2**-H, 2 × C**3**-H), 4.53 (2H, s, C**5**-H_2), 3.48 (1H, dd, *J* = 10.5, 6.0 Hz, C**6**-H_2), 3.37 (1H, dd, *J* = 10.5, 6.5 Hz, C**6**-H_2), 1.80 (1H, m, C**7**-H), 1.58 (1H, m, C**9**-H), 1.28 (1H, m, C**8**-H_2), 0.95 (1H, m, C**8**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.8 (C**10**), 138.2 (C**4**), 128.6, 127.9, 127.8 (C**1**, C**2**, C**3**), 72.9 (C**5**), 71.3 (C**6**), 22.7 (C**7**), 18.4 (C**9**), 13.8 (C**8**); HRMS: (ESI^+) Calculated for $C_{12}H_{14}NaO_3$: 229.0835. Found $[M + Na]^+$: 229.0829.

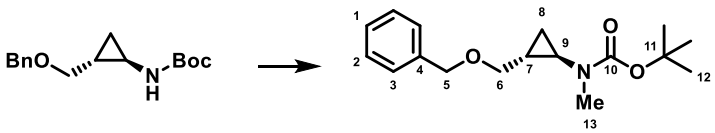
***tert*-Butyl ((1*R**,2*R**)-2-((benzyloxy)methyl)cyclopropyl)carbamate (407a)**



406a 407a

General Procedure D: Carboxylic acid **406a** (9.28 g, 45.0 mmol) was employed and the reaction was heated for 22 h. FCC (10% EtOAc/hexane) provided the title compound (9.60 g, 77%) as a colourless oil; ν_{max} / cm^{-1}: 3353 (w), 2977 (w), 1688 (m), 1509 (m), 1365 (m), 1160 (s), 1096 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.25 (5H, m, C**1**-H, 2 × C**2**-H, 2 × C**3**-H), 4.69 (1H, br. s, NH), 4.53 (2H, d, *J* = 1.5 Hz, C**5**-H_2), 3.47 (1H, dd, *J* = 10.5, 6.5 Hz, C**6**-H_2), 3.30 (1H, dd, *J* = 10.5, 7.0 Hz, C**6**-H_2), 2.42 (1H, br. m, C**9**-H), 1.44 (9H, s, C**12**-H_3), 1.23 (1H, m, C**7**-H), 0.78–0.69 (2H, m, C**8**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5 (C**10**), 138.5 (C**4**), 128.5, 127.9 (C**2**, C**3**), 127.7 (C**1**), 79.5 (C**11**), 72.9 (C**5**), 72.0 (C**6**), 28.5 (C**12**), 28.3 (C**9**), 20.3 (C**7**), 12.3 (C**8**); HRMS: (ESI^+) Calculated for $C_{16}H_{23}NNaO_3$: 300.1576. Found $[M + Na]^+$: 300.1580.

***tert*-Butyl ((1*R**,2*R**)-2-((benzyloxy)methyl)cyclopropyl)(methyl)carbamate (408a)**

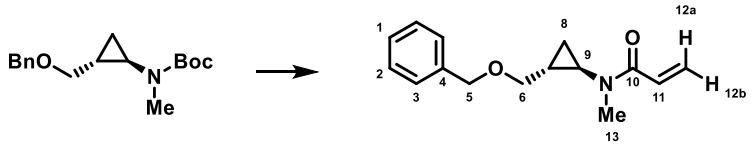


407a 408a

General Procedure G: Carbamate **407a** (9.60 g, 34.0 mmol) was employed in DMF using NaH (1.47 g, 102 mmol) and MeI (10.6 mL, 170 mmol). The reaction was run for 1 h at room temperature. FCC (5% EtOAc/hexane) provided the title compound (6.67 g, 67%) as a colourless oil; ν_{max} / cm^{-1}: 2974 (w), 2856 (w), 1695 (s), 1364 (s), 1152 (s); *The product appears as a 5:2 mixture of rotamers (A:B) in $CDCl_3$*

at room temperature; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.27 (10H, m, 2 × C**1**-H, 4 × C**2**-H, 4 × C**3**-H, A+B), 4.52 (2H, s, C**5**-H_2, A), 4.51 (2H, s, C**5**-H_2, B), 3.69 (1H, dd, *J* = 10.0, 6.0 Hz, C**6**-H_2, B), 3.57 (1H, dd, *J* = 10.0, 6.0 Hz, C**6**-H_2, A), 3.25–3.19 (2H, m, 2 × C**6**-H_2, A+B), 2.85 (3H, s, C**13**-H_3, B), 2.83 (3H, s, C**13**-H_3, A), 2.66 (1H, m, C**9**-H, B), 2.36 (1H, m, C**9**-H, A), 1.44 (9H, s, C**12**-H_3, A), 1.43 (9H, s, C**12**-H_3, B), 1.37–1.28 (2H, m, 2 × C**7**-H, A+B), 1.01 (1H, m, C**8**-H_2, B), 0.87 (1H, m, C**8**-H_2, A), 0.76 (1H, m, C**8**-H_2, A), 0.63 (1H, m, C**8**-H_2, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.9 (C**10**, A), 138.5 (C**4**, A), 128.5, 127.9, 127.7 (C**1**, C**2**, C**3**, A), 79.6 (C**11**, A), 72.8 (C**5**, A), 71.9 (C**6**, A), 35.3 (C**13**, A), 34.8 (C**9**, A), 28.6 (C**12**, A), 28.5 (C**12**, B), 19.1 (C**7**, A), 13.3 (C**8**, A); HRMS: (ESI$^+$) Calculated for $C_{17}H_{26}NO_3$: 292.1907. Found $[M + H]^+$: 292.1911.

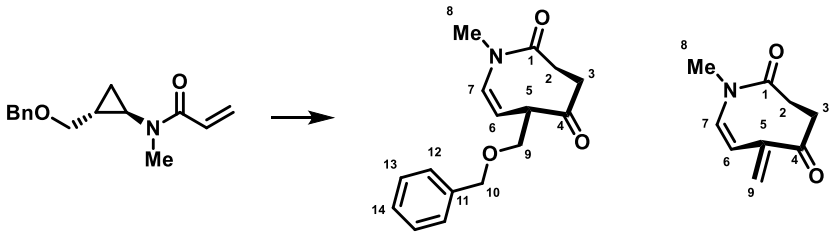
_N_-((1_R*_,2_R*_)-2-((Benzyloxy)methyl)cyclopropyl)-_N_-methylacrylamide (409a)



408a **409a**

General Procedure H: Carbamate **408a** (6.67 g, 22.9 mmol) was employed. FCC (10% EtOAc/hexane) provided the title compound (4.21 g, 75%) as a pale yellow oil; ν_{max} / cm^{-1}: 2860 (w), 2228 (m), 1623 (s), 1614 (m), 1447 (m), 1402 (m), 1073 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.28 (5H, m, C**1**-H, 2 × C**2**-H, 2 × C**3**-H), 7.07 (1H, dd, *J* = 17.0, 10.0 Hz, C**11**-H), 6.33 (1H, dd, *J* = 17.0, 2.0 Hz, C**12a**-H), 5.61 (1H, dd, *J* = 10.0, 2.0 Hz, C**12b**-H), 4.57 (1H, d, *J* = 12.0 Hz, C**5**-H_2), 4.51 (1H, d, *J* = 12.0 Hz, C**5**-H_2), 3.62 (1H, m, C**6**-H_2), 3.23 (1H, m, C**6**-H_2), 2.99 (3H, s, C**13**-H_3), 2.65 (1H, m, C**9**-H), 1.48 (1H, m, C**7**-H), 0.95 (1H, m, C**8**-H_2), 0.86 (1H, m, C**8**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2 (C**10**), 138.3 (C**4**), 129.0 (C**11**), 127.8 , 127.6, 127.6, (C**1**, C**2**, C**3**), 127.4 (C**12**), 73.0 (C**5**), 71.5 (C**6**), 36.3 (C**9**), 34.4 (C**13**), 22.5 (C**7**), 13.6 (C**8**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{19}NNaO_2$: 268.1308. Found $[M + Na]^+$: 268.1311.

(_Z_)-6-((Benzyloxy)methyl)-1-methyl-1,3,4,6-tetrahydroazocine-2,5-dione (410a) _and_ (Z)-1-Methyl-6-methylene-1,3,4,6-tetrahydroazocine-2,5-dione (411)



409a **410a** **411**

To a flame dried reaction tube equipped with a stir bar was added $[Rh(cod)_2]BARF$ (17.7 mg, 0.015 mmol) and $P(p\text{-}CNC_6H_4)_3$ (10.1 mg, 0.300 mmol). The reaction tube was sealed with a rubber septum and purged with argon (balloon) for 30 minutes. Acrylamide **409a** (36.8 mg, 0.150 mmol) in

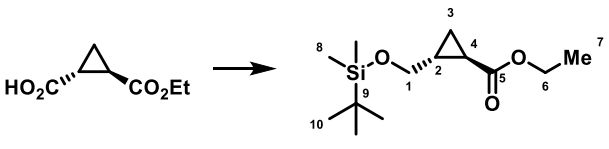
dry benzonitrile (1.5 mL) was added by syringe and the reaction mixture was stirred for 10 seconds. The reaction tube was then purged with CO for 2 minutes and the reaction mixture was sparged for a further 10 seconds before the reaction tube was sealed and heated at 140 °C for 26 h. The resulting solution was transferred to a flask and concentrated *in vacuo* before being analysis by ^{1}H NMR against 1,4-DNB as an internal standard. Purification by FCC (60% EtOAc/hexane) provided the title compound **410a** (11.7 mg, 29%, *contains a number of unidentified impurities*) as a pale brown oil; **Data for major compound 410a:** ν_{max} / cm^{-1}: 3417 (w), 2927 (w), 1712 (m), 1642 (s), 1389 (s), 1169 (s), 1108 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.27 (5H, m, 2 × C**12**-H, 2 × C**13**-H, C**14**-H), 6.21 (1H, dd, *J* = 7.5, 1.0 Hz, C**7**-H), 5.20 (1H, dd, *J* = 9.0, 7.5 Hz, C**6**-H), 4.51 (1H, d, *J* = 12.0 Hz, C**10**-H_2), 4.45 (1H, d, *J* = 12.0 Hz, C**10**-H_2), 3.87 (1H, dd, *J* = 9.5, 7.5 Hz, C**9**-H_2), 3.73 (1H, m, C**5**-H), 3.52 (1H, dd, *J* = 9.5, 6.5 Hz, C**9**-H_2), 3.06 (3H, s, C**8**-H_3), 2.78–2.69 (2H, m, 1 × C**2**-H_2, 1 × C**3**-H_2), 2.57 (1H, m, C**2**-H_2), 2.47 (1H, m, C**3**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.9 (C**4**), 172.7 (C**1**), 138.0 (C**11**), 133.3 (C**7**), 128.5, 127.9, 127.8 (C**12**, C**13**, C**14**), 121.5 (C**6**), 73.5 (C**10**), 68.8 (C**9**), 49.9 (C**5**), 39.3 (C**3**), 34.2 (C**8**), 32.4 (C**2**); HRMS: (ESI$^+$) Calculated for $C_{16}H_{19}NNaO_3$: 296.1257. Found [M + Na]$^+$: 296.1267. **Data for minor compound 411:** *Characteristic signals:* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.92 (1H, d, *J* = 9.0 Hz, C**7**-H), 5.84 (1H, d, *J* = 9.0 Hz, C**6**-H), 5.33 (1H, s, C**9**-H_2), 5.31 (1H, s, C**9**-H_2).

(1*R,2*R**)-2-(Ethoxycarbonyl)cyclopropane-1-carboxylic acid (413)**

413

NaOH (4.00g, 100 mmol) in water (100 mL), was added to a stirring solution of diester (17.6 mL, 100 mmol) in EtOH (125 mL) at 0 °C over 15 min. The reaction was warmed to room temperature and stirred for 4 h. The resulting solution was washed with EtOAc (200 mL), acidified with conc. HCl (pH ~2) and extracted with EtOAc (3 × 100 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to provide the title compound (13.4 g, 85%) as a pale yellow solid; m.p. 54–55 °C ($CHCl_3$) (lit. 56–57 °C)[363]; ν_{max} / cm^{-1}: 2922 (br.), 2632 (w), 1732 (m), 1684 (s), 1379 (m), 1319 (s), 1179 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.16 (2H, q, *J* = 7.0 Hz, C**2**-H_2), 0.22 (1H, m, 1 × C**5**-H_2), 2.17 (1H, m, 1 × C**5**-H_2), 1.53–1.45 (2H, m, 1 × C**4**-H, 1 × C**6**-H), 1.27 (3H, t, *J* = 7.0 Hz, C**1**-H_3); HRMS: (ESI$^+$) Calculated for $C_7H_{10}NaO_4$: 181.0471. Found [M + Na]$^+$: 181.0466.

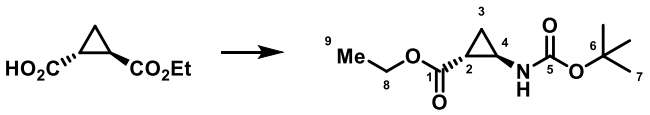
Ethyl (1*R,2*R**)-2-(((tert-butyldimethylsilyl)oxy)methyl)cyclopropane-1-carboxylate (405b)**



413 **405b**

BH_3·THF (70 mL, 70.0 mmol, 1M THF) was added to a stirring solution of carboxylic acid **413** (7.43 g, 47.0 mmol) in THF (67 mL) at 0 °C, over 30 minutes. The resulting solution was warmed to room temperature and stirred for 16 h. The complete reaction mixture was quenched by the careful addition of MeOH until no more effervescence was observed and stirred for 30 minutes. The quenched reaction was concentrated *in vacuo* to provide the crude alcohol. The crude alcohol was dissolved in DMF (47 mL) before the addition of imidazole (3.84 g, 56.4 mmol) and TBSCl (7.44 g, 49.4 mmol). The reaction mixture was stirred for 3 h at room temperature. Water (200 mL) was added and the mixture was extracted with EtOAc (3 × 150 mL). The combined organics were then washed with brine (5 × 150 mL) before being dried over $MgSO_4$ and concentrated *in vacuo*. Purification by FCC (2% EtOAc/hexane) provided the title compound (10.5 g, 86%) as a colourless oil; ν_{max} / cm^{-1}: 2930 (m), 2857 (m), 1728 (s), 1316 (m), 1254 (m), 1178 (s), 1092 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.12 (2H, q, *J* = 7.0 Hz, C**6**-$\underline{H}_2$), 3.66 (1H, dd, *J* = 11.0, 5.0 Hz, 1 × C**1**-$\underline{H}_2$), 3.59 (1H, dd, *J* = 11.0, 5.0 Hz, 1 × C**1**-$\underline{H}_2$), 1.62 (1H, m, C**4**-$\underline{H}$), 1.56 (1H, m, C**2**-$\underline{H}$), 1.25 (3H, t, *J* = 7.0 Hz, C**7**-$\underline{H}_3$), 1.13 (1H, m, 1 × C**3**-$\underline{H}_2$), 0.92–0.88 (10H, m, 1 × C**3**-$\underline{H}_2$, 9 × C**8**-$\underline{H}_3$), -0.04 (6H, s, C**8**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.4 (C**5**), 63.5 (C**1**), 60.5 (C**6**), 26.0 (C**10**), 24.2 (C**4**), 18.4 (C**9**), 17.8 (C**2**), 14.4 (C**7**), 12.4 (C**3**), -5.2 (C**8**); HRMS: (ESI^+) Calculated for $C_{13}H_{26}NaO_3Si$: 281.1543. Found $[M + Na]^+$: 281.1549.

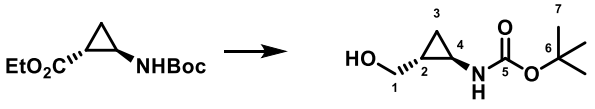
Ethyl (1*R,2*R**)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropane-1-carboxylate (414)**



413 **414**

General Procedure D: Carboxylic acid **413** (4.74 g, 30.0 mmol) was employed and the reaction was heated for 24 h. FCC (10% EtOAc/hexane) provided the title compound (3.89 g, 57%) as a pale yellow oil; ν_{max} / cm^{-1}: 3366 (m), 2990 (m), 1717 (s), 1686 (s), 1511 (s), 1183 (s), 1156 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.70 (1H, br s, N$\underline{H}$), 4.17–4.09 (2H, m, C**8**-$\underline{H}_2$), 3.02 (1H, m, C**4**-$\underline{H}$), 1.71 (1H, m, C**2**-$\underline{H}$), 1.44 (9H, s, C**7**-$\underline{H}_3$), 1.39 (1H, m, 1 x C**3**-$\underline{H}_2$), 1.26 (3H, t, *J* = 7.0 Hz, C**9**-$\underline{H}_3$), 1.09 (1H, m, 1 x C**3**-$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5 (C**1**), 156.0 (C**5**), 80.1 (C**6**), 60.8 (C**8**), 31.9 (C**4**), 28.4 (C**7**), 22.6 (C**2**), 15.8 (C**3**), 14.3 (C**9**); HRMS: (ESI^+) Calculated for $C_{11}H_{19}NNaO_4$: 252.1206. Found $[M + Na]^+$: 252.1212.

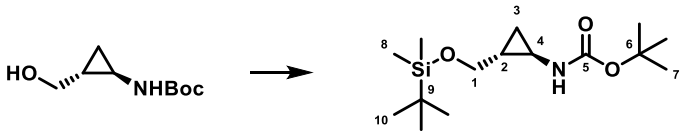
***tert*-Butyl ((1*R**,2*R**)-2-(hydroxymethyl)cyclopropyl)carbamate (415)**



414 **415**

DIBAL-H (19.6 mL, 19.6 mmol, 1 M Hexanes) was added over 10 minutes to a stirring solution of ester **414** (900 mg, 3.93 mmol) in anhydrous PhMe (39 mL) at -78 °C. The reaction was stirred for 3 h before the sequential addition of 10 v% MeOH/PhMe (0.5 ml), MeOH (0.5 mL) and water (10 mL). The reaction was warmed to room temperature and stirred for 30 minutes before being filtered through celite. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (50% EtOAc/hexane) provided the title compound (605 mg, 82%) as a colourless oil; ν_{max} / cm^{-1}: 3318 (br.), 2978 (w), 1686 (s), 1512 (m), 1366 (m), 1164 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.88 (1H, br., N<u>H</u>), 3.81 (1H, br. m, 1 × C**1**-<u>H</u>$_2$), 3.09 (1H, br. m, 1 × C**1**-<u>H</u>$_2$), 2.90 (1H, br., O<u>H</u>), 2.31 (1H, br., C**4**-<u>H</u>), 1.44 (9H, s, C**7**-<u>H</u>$_3$), 1.22 (1H, m, C**2**-<u>H</u>), 0.79 (1H, m, 1 × C**3**-<u>H</u>$_2$), 0.70 (1H, m, 1 × C**3**-<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.2 (C**5**), 80.0 (C**6**), 65.0 (C**1**), 28.6 (C**4**), 28.5 (C**7**), 24.1 (C**2**), 11.4 (C**3**); HRMS: (ESI^+) Calculated for $C_9H_{17}NNaO_3$: 210.1101. Found $[M + Na]^+$: 210.1108.

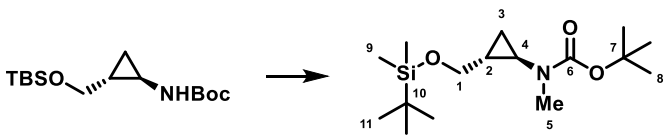
***tert*-Butyl ((1*R**,2*R**)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)carbamate (407b)**



415 **407b**

Imidazole (321 mg, 4.72 mmol) and TBSCl (622 mg, 4.13 mmol) were added to a stirring solution of alcohol **415** (737 mg, 3.94 mmol) in DMF (4.0 mL). On completion, as determined by TLC, the reaction mixture was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (15% EtOAc/hexane) provided the title compound (703 mg, 59%) as a colourless oil; ν_{max} / cm^{-1}: 3330 (br.), 2929 (m), 2857 (m), 1697 (s), 1366 (m), 1252 (s), 1171 (s), 1097 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.69 (1H, br., N<u>H</u>), 3.64 (1H, dd, *J* = 11.0, 5.5 Hz, 1 × C**1**-<u>H</u>$_2$), 3.53 (1H, dd, *J* = 11.0, 5.5 Hz, 1 × C**1**-<u>H</u>$_2$), 2.41 (1H, m, C**4**-<u>H</u>), 1.44 (9H, s, C**7**-<u>H</u>$_3$), 1.12 (1H, m, C**2**-<u>H</u>), 0.88 (9H, s, C**10**-<u>H</u>$_3$), 0.76–0.65 (2H, m, 2 × C**3**-<u>H</u>$_2$), 0.04 (6H, s, C**8**-<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.3 (C**5**), 79.5 (C**6**), 64.1 (C**1**), 28.5 (C**7**), 27.6 (C**4**), 26.1 (C**10**), 25.8 (C**9**), 22.8 (C**2**), 11.7 (C**3**), -5.1 (C**8**); HRMS: (ESI^+) Calculated for $C_{15}H_{31}NNaO_3Si$: 324.1965. Found $[M + Na]^+$: 324.1976.

***tert*-Butyl ((1*R**,2*R**)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)(methyl)carbamate (408b)**

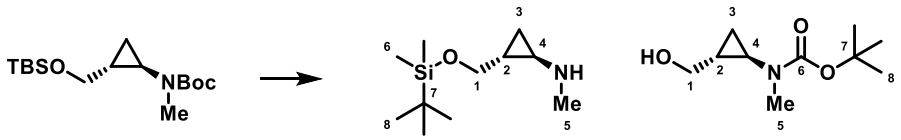


407b **408b**

General Procedure G: Carbamate **407b** (603 mg, 2.00 mmol) was employed in THF using NaH (120 mg, 3.00 mmol) and MeI (0.199 mL, 3.20 mmol). The reaction was run for 16 h at room

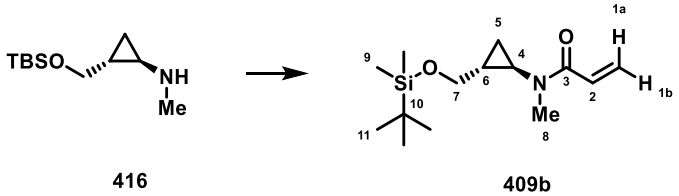
temperature. FCC (2–5% EtOAc/hexane) provided the title compound (400 mg, 63%) as a colourless oil; ν_{max} / cm^{-1}: 2955 (m), 2929 (m), 2860 (m), 1700 (s), 1365 (s), 1252 (m), 1155 (s); *Product **408b** appears as a mixture of rotamers A:B (4:1)*; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.63–3.53 (2H, m, 2 × C**1**-$\underline{H}_2$), 2.82 (3H, s, C**5**-$\underline{H}_3$), 2.34 (1H, m, C**4**-$\underline{H}$), 1.46–1.45 (9H, m, 9 × C**8**-$\underline{H}_3$, A+B), 1.25–1.16 (1H, m, C**2**-$\underline{H}$, A+B), 0.91–0.88 (9H, m, 9 × C**11**-$\underline{H}_3$, A+B), 0.81–0.65 (2H, m, 2 × C**3**-$\underline{H}_2$), 0.09–0.04 (6H, m, C**9**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.0 (C**6**), 80.3 (C**7**, A), 79.5 (C**7**, B), 64.0 (C**1**), 35.5 (C**4**), 34.8 (C**5**), 28.7 (C**8**), 26.1 (C**11**), 24.0 (C**2**), 18.5 (C**10**), 12.6 (C**3**), -3.4 (C**9**, A), -5.1 (C**9**, B); HRMS: (ESI^+) Calculated for $C_{16}H_{33}NNaO_3Si$: 338.2122. Found $[M + Na]^+$: 338.2135.

(1*R,2*R**)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-*N*-methylcyclopropan-1-amine (416) *and tert*-Butyl ((1*R**,2*R**)-2-(hydroxymethyl)cyclopropyl)(methyl)carbamate (417)**



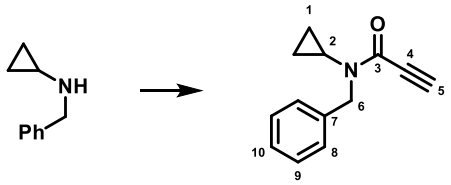
$ZnBr_2$ (2.34 g, 10.4 mmol) was added to a stirring solution of carbamate **408b** (410 mg, 1.30 mmol) in CH_2Cl_2 (13 mL). The reaction mixture was stirred for 16 h before the addition of 1 M aq. NaOH (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (50% EtOAc/Hex then 2% MeOH/EtOAc) provided alcohol **417** (51 mg, 19%) as a yellow oil and amine **416** (44 mg, 15%) as a pale yellow oil; **Data for compound 416:** ν_{max} / cm^{-1}: 3413 (br.), 2974 (w), 1674 (s), 1366 (s), 1157 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.88–3.67 (2H, br. m, 1 × C**1**-$\underline{H}_2$, O$\underline{H}$), 3.01 (1H, br. m, 1 × C**1**-$\underline{H}_2$), 2.80 (3H, s, C**5**-$\underline{H}_3$), 2.33 (1H, m, C**4**-$\underline{H}$), 1.44 (9H, s, C**8**-$\underline{H}_3$), 1.44 (1H, m, C**2**-$\underline{H}$), 0.83 (1H, m, 1 × C**3**-$\underline{H}_2$), 0.67 (1H, m, 1 × C**3**-$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.4 (C**6**), 80.2 (C**7**), 65.1 (C**1**), 36.2 (C**2**), 34.8 (C**5**), 28.5 (C**8**), 25.0 (C**4**), 11.4 (C**3**); HRMS: (ESI^+) Calculated for $C_{10}H_{19}NNaO_3$: 224.1257. Found $[M + Na]^+$: 224.1265. **Data for compound 417:** ν_{max} / cm^{-1}: 2953 (s), 2959 (s), 2856 (s), 1472 (m), 1253 (m), 1098 (s), 836 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.62 (1H, dd, *J* = 11.0, 5.5 Hz, 1 × C**1**-$\underline{H}_2$), 3.32 (1H, dd, *J* = 11.0, 7.5 Hz, 1 × C**1**-$\underline{H}_2$), 2.45 (3H, s, C**5**-$\underline{H}_3$), 1.97 (1H, m, C**4**-$\underline{H}$), 1.02 (1H, m, C**2**-$\underline{H}$), 0.89 (9H, s, C**8**-$\underline{H}_3$), 0.55 (1H, m, 1 × C**3**-$\underline{H}_2$), 0.41 (1H, m, 1 × C**3**-$\underline{H}_2$), 0.05 (6H, s, C**6**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 65.4 (C**2**), 38.1 (C**4**), 36.0 (C**5**), 26.1 (C**8**), 22.7 (C**2**), 18.5 (C**7**), 11.2 (C**3**), -5.0 (C**8**); HRMS: (ESI^+) Calculated for $C_{11}H_{26}NOSi$: 216.1778. Found $[M + Na]^+$: 216.1773.

(1*R,2*R**)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-*N*-methylcyclopropan-1-amine (409b)**



K_2CO_3 (53 mg, 0.380 mmol) and then acryloyl chloride (0.031 mL, 0.380 mmol) were added to a stirring solution of amine **416** (41 mg, 0.190 mmol) in acetone (0.50 mL) and water (0.11 mL) at 0 °C. The reaction was stirred for 6 h before the acetone was removed *in vacuo*. The aqueous layer was diluted with water (4 mL) and extracted with CH_2Cl_2 (3 × 4 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL) before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (20% EtOAc/hexane) provided the title compound (32.1 mg, 63%) as a colourless oil; ν_{max} / cm^{-1}: 2953 (m), 2928 (m), 2856 (m), 1658 (s), 1402 (m), 1256 (m), 1075 (s), 839 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 (1H, dd, *J* = 17.0, 10.0 Hz, C**2**-H), 6.34 (1H, dd, *J* = 17.0, 2.0 Hz, C**1a**-H), 5.64 (1H, dd, *J* = 10.0, 2.0 Hz, C**1b**-H), 3.90 (1H, dd, *J* = 11.0, 4.5 Hz, 1 × C**7**-H_2), 3.26 (1H, dd, *J* = 11.0, 8.0 Hz, 1 × C**7**-H_2), 2.98 (3H, s, C**8**-H_3), 2.63 (1H, m, C**4**-H), 1.39 (1H, m, C**6**-H), 0.90–0.85 (10H, m, 1 × C**5**-H_2, 9 × C11-H_3), 0.81 (1H, m, 1 × C**5**-H_2), 0.07 (3H, s, 3 × C**9**-H_3), 0.06 (3H, s, 3 × C**9**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1 (C**3**), 129.0 (C**2**), 127.2 (C**1**), 64.0 (C**7**), 35.9 (C**4**), 34.3 (C**8**), 25.9 (C**11**), 24.8 (C**6**), 18.3 (C**10**), 12.6 (C**5**), -5.4 (C**9**); HRMS: (ESI^+) Calculated for $C_{14}H_{27}NNaO_2Si$: 292.1703. Found $[M + Na]^+$: 292.1716.

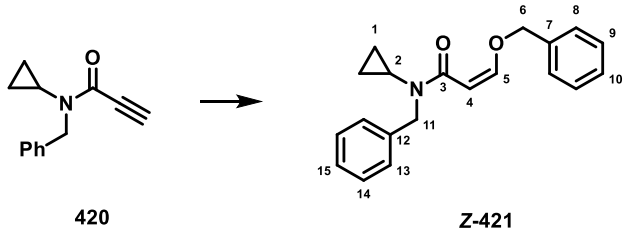
***N*-Benzyl-*N*-cyclopropylpropiolamide (420)**



420

To a stirring solution of benzylcyclopropylamine (1.47 g, 10.0 mmol), DCC (2.27 g, 11.0 mmol) and DMAP (1.2 mg, 0.01 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added propiolic acid (0.67 mL, 10.8 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred for 2 h before being filtered through a pad of celite, washing with CH_2Cl_2 (2 × 10 mL). The organic solution was concentrated *in vacuo*. FCC (15% EtOAc/hexane) provided the title compound (2.19 g, 110%) as a pale yellow oil; m.p. 102–105 °C ($CHCl_3$); ν_{max} / cm^{-1}: 3206 (m), 2096 (m), 1615 (s), 1395 (m), 1303 (m); *Product appears as a 3:1 mixture of rotamers (A:B) in $CDCl_3$;* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.25 (10H, m, C**8**-H, C**9**-H, C**10**-H, A+B), 4.77 (2H, s, C**6**-H_2, B), 4.60 (2H, s, C**6**-H_2, A), 3.20 (1H, s, C**5**-H, A), 3.08 (1H, s, C**5**-H, B), 2.66 (1H, m, C**2**-H, A), 2.52 (1H, m, C**2**-H, B), 0.88–0.87 (4H, m, C**1**-H_2, A), 0.82 (2H, m, C**1**-H_2, B), 0.69 (2H, m, C**1**-H_2, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0 (C**3**, A), 155.3 (C**3**, B), 137.0 (C**7**, A), 136.9 (C**7**, B), 128.9, 128.7, 128.2, 127.9, 127.6, 127.4 (C**8**, C**9**, C**10**, A+B), 80.1 (C**5**, A), 78.7 (C**4**, A), 77.2 (C**5**, B), 76.7 (C**4**, B), 53.6 (C**6**, B), 49.9 (C**6**, A), 30.4 (C**2**, A), 28.2 (C**2**, B), 9.33 (C**1**, A), 7.2 (C**1**, B); HRMS: (ESI^+) Calculated for $C_{13}H_{14}NO$: 200.1070. Found $[M + H]^+$: 200.1064.

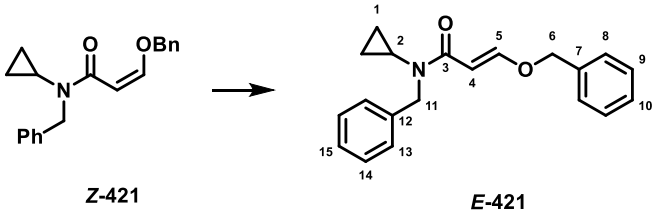
(*Z*)-*N*-Benzyl-3-(benzyloxy)-*N*-cyclopropylacrylamide (*Z*-421)



420 **Z-421**

To a stirring solution of AgOTf (5.1 mg, 0.020 mmol) in BnOH (0.5 mL) in a flame-dried flask under an atmosphere of argon was added amide **420** (300 mg, 2.00 mmol) in BnOH (0.3 mL). The reaction mixture was heated at 70 °C for 3 h before being purified by FCC (30% EtOAc/hexane) to afford the title compound (401 mg, 65%) as a yellow oil. *The Z-geometry of the product alkene was determined by comparison of the coupling constants of the C**4**-H and C**5**-H protons with those measured in compound **E**-**421** (see below)*; ν_{max} / cm^{-1}: 1655 (s), 1614 (s), 1454 (m), 137 (m), 1263 (m), 1105 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.20 (10H, m, C**8**-H, C**9**-H, C**10**-H, C**13**-H, C**14**-H, C**15**-H), 6.46 (1H, d, *J* = 7.0 Hz, C**5**-H), 5.47 (1h, d, *J* = 7.0 Hz, C**4**-H), 5.03 (2H, s, C**6**-H_2), 4.64 (2H, s, C**11**-H_2), 2.53 (1H, m, C**2**-H), 0.75–0.73 (4H, m, C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7 (C**3**), 154.3 (C**5**), 138.7 (C**12**), 136.6 (C**7**), 128.8, 128.5, 128.4, 128.2, 127.7, 127.0 (C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 99.2 (C**4**), 75.8 (C**6**), 49.5 (C**11**), 29.8 (C**2**), 9.5 (C**1**); HRMS: (ESI^+) Calculated for $C_{20}H_{22}NO_2$: 308.1645. Found $[M + H]^+$: 308.1649.

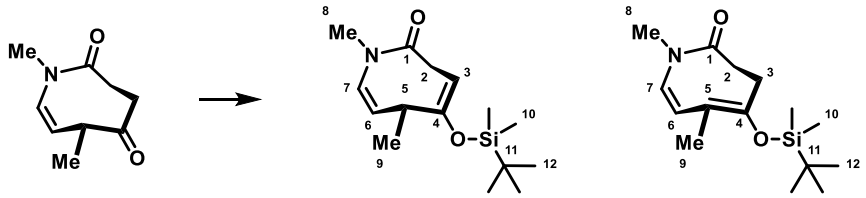
(*E*)-*N*-Benzyl-3-(benzyloxy)-*N*-cyclopropylacrylamide (*E*-421)



Z-421 **E-421**

General Procedure I: Acrylamide ***Z*-421** (46.1 mg, 0.150 mmol) and $[Rh(cod)_2]BARF$ (17.7 mg, 0.015 mmol), P(*p*-$CNC_6H_4)_3$ (5.06 mg, 0.015 mmol) were employed, and the reaction was heated at 150 °C for 4 h. The reaction mixture was concentrated *in vacuo* and purified by FCC (25% EtOAc/hexane) afforded the title compound (27 mg, 59%) as an orange oil; ν_{max} / cm^{-1}: 1652 (s), 1596 (s), 1403 (m), 1372 (m), 1164 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (1H, d, *J* = 12.0 Hz, C**5**-H), 7.38–7.18 (10H, m, C**8**-H, C**9**-H, C**10**-H, C**13**-H, C**14**-H, C**15**-H), 6.13 (1H, d, *J* = 12.0 Hz, C**4**-H), 4.93 (2h, s, C**6**-H_2), 4.62 (2H, s, C**11**-H_2), 2.51 (1H, m, C**2**-H), 0.80–0.69 (4H, m, C**1**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.3 (C**3**), 160.9 (C**5**), 138.5 (C**12**), 135.7 (C**7**), 128.7, 128.4, 128.4, 127.7, 127.7, 126.9 (C**8**, C**9**, C**10**, C**13**, C**14**, C**15**), 98.6 (C**4**), 73.4 (C**6**), 49.8 (C**11**), 29.5 (C**2**), 9.4 (C**1**); HRMS: (ESI^+) Calculated for $C_{20}H_{22}NO_2$: 308.1645. Found $[M + H]^+$: 308.1653.

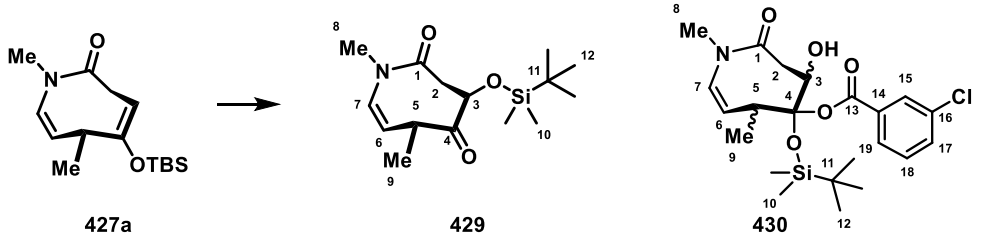
(4*E*,7*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-1,6-dimethyl-3,6-dihydroazocin-2(1*H*)-one (427a) ***and*** **(5*E*,7*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-1,6-dimethyl-3,4-dihydroazocin-2(1*H*)-one (427b)**



403a 427a 427b

Freshly prepared LDA (3.94 mL, 0.5 M, 1.97 mmol), DMPU (0.24 mL, 1.97 mmol) and THF (0.82 mL) were added to a flame-dried flask fitted with a septum under an atmosphere of argon. The mixture was cooled to -78 °C before the addition of ketone **403a** (220 mg, 1.32 mmol) in THF (2 mL) over 1 minute. After 15 minutes, TBSCl (995 mL, 6.60 mmol) in THF (1 mL) was added and the reaction was warmed to room temperature. Upon consumption of the starting material by TLC (after approximately 2 h) the reaction was quenched with water (10 mL). The aqueous was extracted with EtOAc (3 × 15 mL) and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by FCC (20% EtOAc/hexane) provided the title compound (260 mg, 70%, 8:1 mixture of regioisomers **427a**:**427b**) as a pale yellow oil; **Data for the major regioisomer 427a**: ν_{max} / cm^{-1}: 2955 (m), 2929 (m), 2857 (m), 1648 (s), 1340 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): 6.12 (1H, d, *J* = 7.5 Hz, C**7**-H), 5.15 (1H, dd, *J* = 8.5, 7.5 Hz, C**6**-H), 4.88 (1H, dd, *J* = 7.0, 7.0 Hz, C**3**-H), 3.08 (1H, m, C**5**-H), 3.04–2.96 (2H, m, C**2**-H_2), 2.94 (3H, s, C**8**-H_3), 1.16 (3H, d, *J* = 7.0 Hz, C**9**-H_3), 0.91 (9H, s, C**12**-H_3), 0.15 (3H, s, C**10**-H_3), 0.14 (3H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5 (C**1**), 151.7 (C**4**), 130.3 (C**7**), 124.5 (C**6**), 100.0 (C**3**), 35.4 (C**5**), 34.3 (C**2**), 33.1 (C**8**), 25.9 (C**12**), 18.3 (C**11**), 17.5 (C**9**), -4.4 (C**10**), -4.5 (C**10**); HRMS: (ESI^+) Calculated for $C_{15}H_{28}NO_2Si$: 282.1884. Found $[M + H]^+$: 282.1897. **Data for the minor regioisomer 427b**: *Characteristic signals only*; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.76 (1H, d, *J* = 9.0 Hz, C**7**-H), 5.50 (1H, d, *J* = 9.0 Hz, C**6**-H), 2.99 (3H, s, C**8**-H_3), 1.67 (3H, s, C**9**-H_3), 0.94 (9H, s, C**12**-H_3), 0.15 (6H, s, C**10**-H_3);

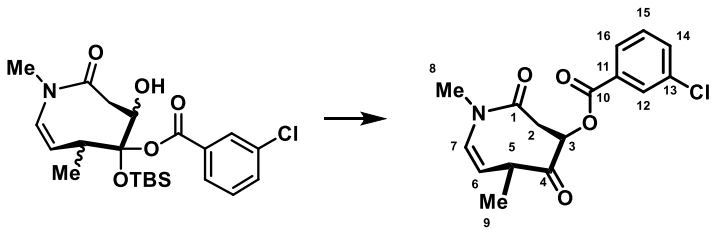
(*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-1,6-dimethyl-1,3,4,6-tetrahydroazocine-2,5-dione (429) ***and*** **(*R*,Z*)-5-((tert-butyldimethylsilyl)oxy)-4-hydroxy-1,6-dimethyl-2-oxo-1,2,3,4,5,6-hexahydroazocin-5-yl 3-chlorobenzoate (430)**



427a 429 430

$NaHCO_3$ (33.0 mg, 0.390 mmol) was added to a flame-dried reaction tube which was sealed and purged with argon. Silyl enol ether **427a** (100 mg, 0.350 mmol) in CH_2Cl_2 (3.5 mL) was added by syringe and the reaction mixture was cooled to 0 °C. *m*-CPBA (67.4 mg, 0.390 mmol) in CH_2Cl_2 (1.0 mL) was added by syringe in one portion. The reaction was stirred for 45 minutes before being diluted with CH_2Cl_2 (5 mL) and washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* before purification by FCC (15% EtOAc/hexane) provided the title compounds (41 mg, 39%, 4:1 mixture of **429**:**430**) as a colourless oil; **Data for product 429:** *The relative stereochemistry of product **429** was not determined*; ν_{max} / cm^{-1}: 2956 (m), 2928 (m), 2855 (m), 1732 (s), 1649 (s), 1254 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.10 (1H, dd, *J* = 7.5, 1.0 Hz, C**7**-H, A), 5.94 (1H, dd, *J* = 8.0, 1.0 Hz, C**7**-H, B), 5.24 (1H, d, *J* = 7.5 Hz, C**6**-H, B), 5.22 (1H, d, *J* = 7.5 Hz, C**6**-H, A), 5.02 (1H, d, *J* = 9.0 Hz, C**3**-H, B), 4.48 (1H, dd, *J* = 12.0, 3.5 Hz, C**3**-H, A), 3.47 (1H, dqd, *J* = 9.0, 6.5, 1.0 Hz, C**5**-H, A), 3.23 (1H, d, *J* = 13.0 Hz, C**2**-H_2, B), 3.12 (1H, dd, *J* = 12.0, 12.0 Hz, C**2**-H_2, A), 3.05 (6H, s, 6 × C**8**-H_3, A+B), 2.83 (1H, dd, *J* = 13.0, 9.0 Hz, C**2**-H_2, B), 2.70 (1H, m, *J* = 7.5 Hz, C**5**-H, B), 2.67 (1H, dd, *J* = 12.0, 3.5 Hz, C**2**-H_2, A), 1.17 (3H, d, *J* = 6.5 Hz, C**9**-H_3, A), 1.12 (3H, d, *J* = 7.5 Hz, C**9**-H_3, B), 0.92 (9H, s, C**12**-H_3, A), 0.90 (9H, s, C**12**-H_3, B), 0.24 (3H, s, C**10**-H_3, B), 0.22 (3H, s, C**10**-H_3, B), 0.16 (3H, s, C**10**-H_3, A), 0.06 (3H, s, C**10**-H_3 A); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.2 (C**4**, A), 171.0, 168.5 (C**1**, A+B), 131.6 (C**7**, A), 130.0 (C**6**, B), 128.4 (C**7**, B), 126.7 (C**6**, A), 74.5 (C**3**, B), 74.1 (C**3**, A), 43.2 (C**2**, A), 40.8 (C**5**, A), 36.5 (C**5**, B), 34.2 (C**2**, B), 34.2, 34.1 (C**8**, A+B), 26.0 (C**12**, B), 25.9 (C**12**, A), 18.6 (C**11**, A), 18.2 (C**11**, B), 15.4 (C**9**, A), 15.2 (C**9**, B), -2.2 (C**10**, B), -2.4 (C**10**, B), -4.5 (C**10**, A), -5.4 (C**10**, A); HRMS: (ESI^+) Calculated for $C_{15}H_{28}NO_3Si$: 298.1833. Found $[M + H]^+$: 298.1832. **Data for acetal 430:** *The relative stereochemistry of product **430** was not determined*; m.p. 120–121 °C (CH_2Cl_2); ν_{max} / cm^{-1}: 3367 (br.), 2929 (w), 1731 (m), 1633 (s), 1251 (s), 1069 (s), 1027 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (1H, s, C**15**-H), 8.00 (1H, d, *J* = 8.0 Hz, C**17**/**19**-H), 7.54 (1H, m, C**17**/**19**-H), 7.40 (1H, dd, *J* = 8.0, 8.0 Hz, C**18**-H), 5.93 (1H, d, *J* = 8.0 Hz, C**7**-H), 5.23 (1H, dd, *J* = 8.5, 8.0 Hz, C**6**-H), 5.02 (1H, d, *J* = 9.0 Hz, C**3**-H), 3.58 (1H, s, OH), 3.23 (1H, d, *J* = 13.0 Hz, 1 × C**2**-H_2), 3.05 (3H, s, C**8**-H_3), 2.83 (1H, dd, *J* = 13.0, 9.0 Hz, 1 × C**2**-H_2), 2.70 (1H, m, C**5**-H), 1.12 (3H, d, *J* = 7.0 Hz, C**9**-H_3), 0.90 (9H, s, C**12**-H_3), 0.24 (3H, s, C**10**-H_3), 0.22 (3H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5 (C**1**), 166.9 (C**13**), 134.7, 133.6, 131.6, 130.3, 130.0, 129.9, 128.5, 128.4 (ArC, C**6**, C**7**), 97.9 (C**4**), 74.5 (C**3**), 36.5 (C**5**), 34.2 (C**2**), 34.1 (C**8**), 26.0 (C**12**), 18.2 (C**11**), 15.2 (C**9**), -2.2 (C**10**), -2.4 (C**10**); HRMS: (ESI^+) Calculated for $C_{22}H_{32}ClNNaO_5Si$: 476.1630. Found $[M + Na]^+$: 476.1638.

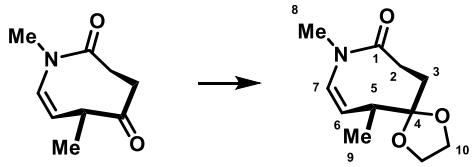
(*Z*)-1,6-Dimethyl-2,5-dioxo-1,2,3,4,5,6-hexahydroazocin-4-yl 3-chlorobenzoate (432)



430 **432**

DBU (0.10 mL, 0.65 mmol) was added to a stirring solution of acetal **430** (150 mg, 4:1 **429**:**430**, 0.090 mmol of acetal **430**) in CH_2Cl_2 (1.1 mL) at 0 °C. The reaction was stirred for 15 minutes by which time the starting material had been consumed as determined by TLC. The reaction was concentrated *in vacuo* and purified by FCC (25% EtOAc/hexane) to provide the title compound (22.5 mg, 77%) as a colourless oil. *The relative stereochemistry of product **432** was not determined*; ν_{max} / cm^{-1}: 2938 (w), 1722 (s), 1658 (s), 1645 (s), 1384 (m), 1289 (s), 1253 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, dd, *J* = 2.0, 2.0 Hz, C**12**-H), 7.93 (1H, d, *J* = 8.0 Hz, C**14**/**16**-H), 7.54 (1H, m, C**14**/**16**-H), 7.38 (1H, dd, *J* = 8.0, 8.0 Hz, C**15**-H), 6.17 (1H, d, *J* = 7.5 Hz, C**7**-H), 5.64 (1H, dd, *J* = 12.5, 3.0 Hz, C**3**-H), 5.30 (1H, dd, *J* = 8.5, 7.5 Hz, C**6**-H), 3.62 (1H, m, C**5**-H), 3.30 (1H, dd, *J* = 12.5, 12.0 Hz, 1 × C**2**-H_2), 3.10 (3H, s, C**8**-H_3), 2.90 (1H, dd, *J* = 12.0 3.0 Hz, 1 × C**2**-H_2), 1.23 (3H, d, *J* = 6.5 Hz, C**9**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.1 (C**4**), 169.5 (C**1**), 164.3 (C**10**), 134.7 (C**11**), 133.5 (C**14**/**16**), 131.8 (C**7**), 131.1 (C**13**), 130.0, 129.9 (C**12**, C**15**), 128.2 (C**14**/**16**), 126.5 (C**6**), 74.5 (C**3**), 41.0 (C**5**), 38.6 (C**2**), 34.5 (C**8**), 24.0 (C**9**); HRMS: (ESI^+) Calculated for $C_{16}H_{16}ClNNaO_4$: 344.0660. Found $[M + Na]^+$: 3440.0661.

(*Z*)-9,12-Dimethyl-1,4-dioxa-9-azaspiro[4.7]dodec-10-en-8-one (434)

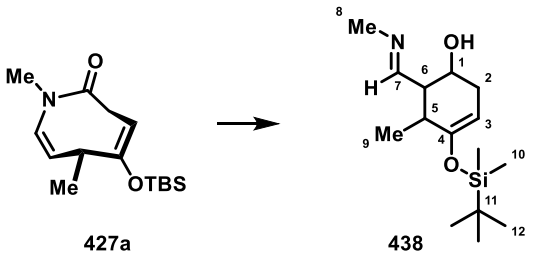


403a **434**

$BF_3{\cdot}Et_2O$ (0.22 mL, 0.18 mmol) was added to a stirring solution of ketone **403a** (200 mg, 1.20 mmol) and ethylene glycol (0.22 mL, 1.80 mmol) in CH_2Cl_2 (2.4 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 2 h before the addition of water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the title compound (234 mg, 92%) as an orange oil; ν_{max} / cm^{-1}: 2893 (w), 1634 (s), 1388 (m), 1161 (m), 1072 (m), 1044 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.96 (1H, dd, *J* = 8.0, 1.0 Hz, C**7**-H), 5.22 (1H, m, C**6**-H), 4.00 (2H, m, 1 × C**10a**-H_2, 1 × C**10b**-H_2), 3.83 (2H, m, 1 × C**10a**-H_2, 1 × C**10b**-H_2), 2.97 (3H, s, C**8**-H_3), 2.70 (1H, m, 1 × C**3**-H_2), 2.52 (1H, m, C**5**-H), 2.33 (1H, m, 1 × C**3**-H_2), 1.95–1.79 (2H, m, 2 × C**2**-H_2), 1.01 (3H, d, *J* = 7.0 Hz, C**9**-H_3); ^{13}C NMR ($CDCl_3$,

100 MHz): δ 173.9 (C**1**), 129.5 (C**7**), 129.4 (C**6**), 110.1 (C**4**), 65.6, 64.6 (C**10a**, C**10b**), 39.1 (C**5**), 34.5 (C**2**), 33.7 (C**8**), 31.2 (C**3**), 15.1 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{11}H_{18}NO_3$: 212.1281. Found [M + H]$^+$: 212.1284.

(*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-methyl-6-((methylimino)methyl)cyclohex-3-en-1-ol (438)



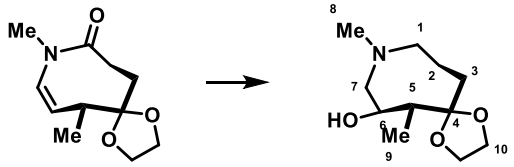
$LiAlH_4$ (0.039 mL, 2 M in THF, 0.078 mmol) was added to amide **427a** (20 mg, 0.071 mmol) in anhydrous THF (0.7 mL) at 0 °C, over 30 seconds. TLC indicated the reaction was complete after 5 minutes. The reaction was diluted with Et_2O (1.0 mL), before being quenched by the addition of water (0.1 mL) then 3 M aq. NaOH (0.1 mL) and then water (0.3 mL). The reaction was stirred for 15 minutes before being diluted with water (1 mL) and extracted with Et_2O (3 × 2 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound (19.0 mg, 95%) as a pale yellow oil. *The relative stereochemistry of product was not determined*; ν_{max} / cm^{-1}: 3342 (br.), 2930 (m), 1665 (w), 1345 (m), 1192 (s), 1181 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (1H, m, C**7**-H), 4.66 (1H, dd, *J* = 4.0, 4.0 Hz, C**3**-H), 4.08 (1H, m, C**1**-H), 3.28 (3H, m, C**8**-H_3), 2.41–2.30 (6H, m, 1 × C**2**-H_2, 1 × C**5**-H, 1 × C**6**-H), 2.16 (1H, m, 1 × C**2**-H_2), 1.19 (3H, d, *J* = 6.5 Hz, C**9**-H_3), 0.92 (9H, s, C**12**-H_3), 0.14 (6H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2 (C**7**), 152.6 (C**4**), 99.7 (C**3**), 65.8 (C**1**), 49.8 (C**6**), 47.8 (C**8**), 36.2 (C**5**), 30.6 (C**2**), 25.7 (C**12**), 18.2 (C**11**), 17.5 (C**10**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{30}NO_2Si$: 284.2040. Found [M + H]$^+$: 284.2044.

11-Bromo-10-methoxy-9,12-dimethyl-1,4-dioxa-9-azaspiro[4.7]dodecan-8-one (449)

NBS (18.7 mg, 0.105 mmol) was added to a stirring solution of enamide **434** (20.0 mg, 0.095 mmol) and MeOH (0.080 mL, 0.190 mmol) in THF (0.50 mL) at -78 °C. The reaction was warmed to room temperature after 1 h before being concentrated *in vacuo*. FCC (90% EtOAc/hexane) provided the title compound (26.0 mg, 86%, 6:1 d.r.) as a pale yellow oil; **Data for the mixture of diastereomers:** ν_{max} / cm^{-1}: 2889 (w), 1623 (s), 1395 (m), 1076 (s); **Data for the major diastereomer:** *The relative stereochemistry of the major diastereomer was not determined*; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.87

(1H, d, *J* = 10.0 Hz, C**7**-H), 4.18 (1H, m, 1 × C**10a**-H$_2$), 4.05 (1H, d, *J* = 10.0 Hz, C**6**-H), 3.99–3.90 (3H, m, 1 × C**10a**-H$_2$, 2 × C**10b**-H$_2$), 2.89 (1H, m, 1 × C**2**-H$_2$), 2.81 (3H, s, C**8**-H$_3$), 2.75 (1H, m, C**5**-H), 2.75 (3H, s, C**11**-H$_3$), 2.41 (1H, ddd, *J* = 13.5, 6.5, 2.0 Hz, 1 × C**2**-H$_2$), 2.20 (1H, ddd, *J* = 16.5, 14.5, 2.0 Hz, 1 × C**3**-H$_2$), 1.75 (1H, m, 1 × C**3**-H$_2$), 0.97 (3H, d, *J* = 8.0 Hz, C**9**-H$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.8 (C**1**), 111.8 (C**4**), 80.6 (C**7**), 66.0, 64.4 (C**10a**, C**10b**), 57.1 (C**5**), 34.3 (C**3**), 30.8 (C**2**), 29.7 (C**11**), 26.2 (C**8**), 17.7 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{11}H_{17}BrNO_3$: 290.0386. Found $[M + H]^+$: 290.0407.

6,9-Dimethyl-1,4-dioxa-9-azaspiro[4.7]dodecan-7-ol (451)

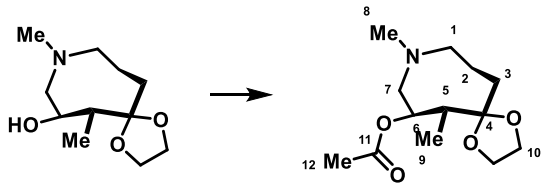


434 **451**

BH_3·THF (1.42 mL, 1.42 mmol) was added to a stirring solution of enamide **434** (100 mg, 0.47 mmol) in THF (2.35 mL) at -78 °C. The reaction was stirred for 10 minutes before warming to room temperature and stirring for a further 1.5 h by which time enamide **434** had been consumed by TLC. The reaction was cooled to 0 °C and quenched by the addition of water (1 mL) followed by 2 M aq. NaOH (1.5 mL) and 30% aq. H_2O_2 (1.0 mL). After 30 minutes the aqueous layer was saturated by the addition of K_2CO_3 and then extracted with Et_2O (3 × 5 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. FCC (40% EtOAc/hexane) provided the major diastereomer of the title compound (23 mg, 22%) as a pale yellow oil and the minor diastereomer (18 mg, 18%) as pale yellow oil; *The product diastereomers are formed in a 1:1 ratio and are easily separated by FCC;* **Data for the first diastereomer (A) to elute by FCC:** *The relative stereochemistry of diastereomer A was not determined*; ν_{max} / cm^{-1}: 3488 (br.), 2349 (m), 1455 (m), 1167 (s), 1058 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.96–3.79 (6H, m, 1 × C**6**-H, 1 × C**7**-H$_2$, 2 × C**10a**-H$_2$, 2 × C**10b**-H$_2$), 3.20 (1H, dd, *J* = 15.0, 10.0 Hz, 1 × C**1**-H$_2$), 2.90 (1H, dd, *J* = 15.0, 7.0 Hz, 1 × C**1**-H$_2$), 2.71 (1H, d, *J* = 14.0 Hz, 1 × C**7**-H$_2$), 2.55 (3H, s, C**8**-H$_3$), 1.94–1.82 (3H, m, 1 × C**2**-H$_2$, 1 × C**3**-H$_2$, 1 × C5-H), 1.75–1.61 (2H, m, 1 × C**2**-H$_2$, 1 × C3-H$_2$), 1.14 (3H, d, *J* = 7.0 Hz, C**9**-H$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 111.0 (C**4**), 69.6 (C**6**), 65.1 (C**7**), 64.6, 63.7 (C**10a**, C**10b**), 61.4 (C**1**), 51.7 (C**8**), 46.1 (C**5**), 34.7 (C**2**), 18.5 (C**3**), 14.3 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{11}H_{22}NO_3$: 216.1594. Found $[M + H]^+$: 216.1594. **Data for the second diastereomer (B) to elute by FCC:** *The relative stereochemistry of diastereomer B was not determined*; ν_{max} / cm^{-1}: 3277 (br.), 2376 (m), 1446 (m), 1161 (s), 1066 (s), 1034 (s), 1019 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.98–3.82 (5H, m, 1 × C**7**-H$_2$, 2 × C**10a**-H$_2$, 2 × C**10b**-H$_2$), 3.56 (1H, d, *J* = 9.5 Hz, C**6**-H), 3.13 (1H, dd, *J* = 13.5, 7.0 Hz, 1 × C**1**-H$_2$), 2.94 (1H, d, *J* = 15.0 Hz, 1 × C**7**-H$_2$), 2.85 (1H, dd, *J* = 13.5, 10.5 Hz, 1 × C**1**-H$_2$), 2.63 (3H, s, C**8**-H$_3$), 2.20 (1H, m, 1 × C**2**-H$_2$), 1.95 (1H, m, C**5**-H), 1.82–1.77 (2H, m, 2 × C**3**-H$_2$), 1.65 (1H, m, 1 × C**2**-H$_2$), 1.12 (3H, d, *J* = 6.5 Hz, C**9**-H$_3$); ^{13}C NMR ($CDCl_3$,

100 MHz): δ 110.6 (C**4**), 69.69 (C**6**), 64.7, 64.5 (C**10a**, C**10b**), 63.9 (C**7**), 60.8 (C**1**), 51.8 (C**8**), 48.2 (C**5**), 35.4 (C**3**), 19.5 (C**2**), 13.7 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{11}H_{22}NO_3$: 216.1594. Found [M + H]$^+$: 216.1589.

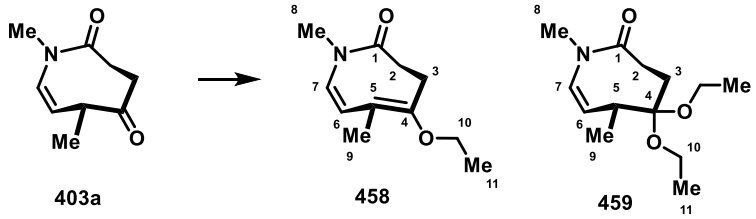
6,9-Dimethyl-1,4-dioxa-9-azaspiro[4.7]dodecan-7-yl acetate (454)



451 454

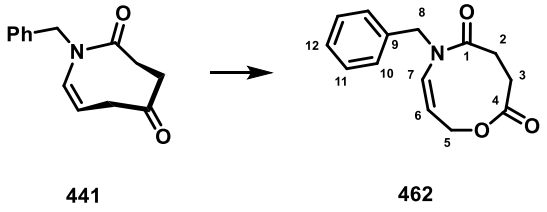
Acetic anhydride (0.019 mL, 0.20 mmol) was added to a stirring solution of alcohol **451** (21 mg, 0.10 mmol, 1:1 d.r.), DMAP (1.2 mg, 0.010 mmol) and NEt_3 (0.035 mL, 0.25 mmol) in CH_2Cl_2 (1.0 mL). Water (2 mL) was added after 16 h and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. FCC (30% EtOAc/hexane) provided the minor diastereomer of the title compound (8.0 mg, 31%) and the major diastereomer (12.3 mg, 48%) as colourless oils; **Data for the first diastereomer (A) to elute by FCC:** ν_{max} / cm^{-1}: 2888 (m), 2388 (m), 2362 9m), 1730 (s), 1374 (m), 1256 (s), 1181 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.10 (1H, ddd, *J* = 11.0, 5.0, 2.0 Hz, C**6**-H), 4.10 (1H, dd, *J* = 16.0, 5.0 Hz, 1 × C**7**-H$_2$), 3.99–3.84 (4H, m, 2 × C**10a**-H$_2$, 2 × C**10b**-H$_2$), 3.08–2.94 (2H, m, 2 × C**1**-H$_2$), 2.78 (1H, d, *J* = 16.0 Hz, 1 × C**7**-H$_2$), 2.61 (3H, s, C**8**-H$_3$), 2.32 (1H, m, 1 × C**2**-H$_2$), 2.09 (3H, s, C**12**-H$_3$), 2.01 (1H, m, C**5**-H), 1.94–1.82 (2H, m, 2 × C**3**-H$_2$), 1.66 (1H, m, 1 × C**2**-H$_2$), 0.93 (3H, d, *J* = 7.0 Hz, C**9**-H$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0 (C**11**), 110.4 (C**4**), 69.6 (C**6**), 64.8, 64.4 (C**10a**, C**10b**), 63.2 (C**7**), 60.0 (C**1**), 51.5 (C**8**), 46.7 (C**5**), 34.4 (C**3**), 21.2 (C**12**), 20.1 (C**2**), 13.0 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{23}NNaO_4$: 280.1519. Found [M + Na]$^+$: 280.1532. **Data for the second diastereomer (B) to elute by FCC:** ν_{max} / cm^{-1}: 2944 (m), 2372 (m), 1745 (s), 1372 (m), 1231 (s), 1166 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.14 (1H, m, C**6**-H), 3.97–3.86 (4H, m, 2 × C**10a**-H$_2$, 2 × C**10b**-H$_2$), 3.55 (1H, d, *J* = 15.0 Hz, 1 × C**7**-H$_2$), 3.30–3.20 (2H, m, 1 × C**1**-H$_2$, 1 × C**7**-H$_2$), 2.95 (1H, m, 1 × C**1**-H$_2$), 2.63 (3H, s, C**8**-H$_3$), 2.17 (1H, m, C**5**-H), 2.08 (3H, s, C**12**-H$_3$), 1.96 (1H, m, 1 × C**3**-H$_2$), 1.91–1.85 (2H, m, 2 × C**2**-H$_2$), 1.72 (1H, m, 1 × C**3**-H$_2$), 0.97 (3H, d, *J* = 7.0 Hz, C**9**-H$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7 (C**11**), 110.6 (C**4**), 72.8 (C**6**), 64.6, 64.6 (C**10a**, C**10b**), 61.5 (C**7**), 60.3 (C**1**), 52.4 (C**8**), 45.8 (C**5**), 35.7 (C**3**), 21.4 (C**12**), 18.9 (C**2**), 13.7 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{23}NNaO_4$: 280.1519. Found [M + Na]$^+$: 280.1527.

(5*E*,7*Z*)-5-Ethoxy-1,6-dimethyl-3,4-dihydroazocin-2(1*H*)-one (458) *and* (*Z*)-5,5-Diethoxy-1,6-dimethyl-3,4,5,6-tetrahydroazocin-2(1*H*)-one (459)



p-TSA (5.2 mg, 0.030 mmol) was added to a stirring solution of ketone **403a** (50 mg, 0.30 mmol) and triethyl orthoformate (0.15 mL, 0.90 mmol) in EtOH (0.6 mL) at room temperature. The reaction was stirred for 16 h before being concentrated *in vacuo*. The crude reaction mixture was dissolved in water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide title compounds (32 mg, 2:1 **458**:**459**, 34% yield for **458**, 17% yield for **459**) as a pale yellow oil; **Data for the enol ether 458:** ν_{max} / cm^{-1}: 2924 (w), 1734 (s), 1435 (m), 1165 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.78 (1H, d, *J* = 9.0 Hz, C**7**-H), 5.50 (1H, d, *J* = 9.0 Hz, C**6**-H), 3.74 (2H, q, *J* = 7.0 Hz, C**10**-H_2), 2.98 (3H, s, C**8**-H_3), 2.71–2.62 (4H, m, 2 × C**2**-H_2, 2 × C**3**-H_2), 1.69 (3H, d, *J* = 1.5Hz, C**9**-H_3), 1.23 (3H, t, *J* = 7.0 Hz, C**11**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.7 (C**1**), 151.0 (C**4**), 126.7 (C**7**), 122.9 (C**6**), 112.7 (C**5**), 64.3 (C**10**), 33.9 (C**8**), 30.6, 28.7 (C**2**, C**3**), 18.7 (C**9**), 15.6 (C**11**); HRMS: (ESI^+) Calculated for $C_{11}H_{18}NO_2$: 196.1332. Found $[M + H]^+$: 196.1334. **Data for the diethyl acetal 459:** *Characteristic signals only*; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.90 (1H, br. m, C**7**-H), 2.95 (3H, s, C**8**-H_3).

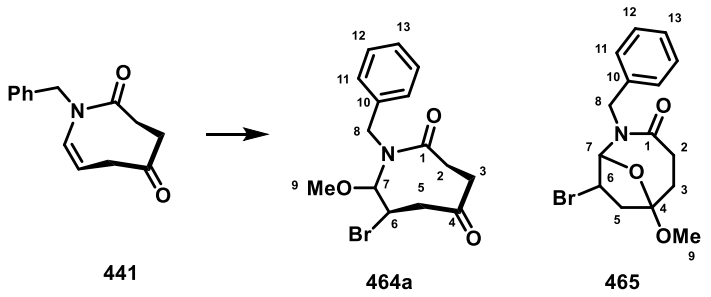
(*Z*)-5-Benzyl-2,5,7,8-tetrahydro-1,5-oxazonine-6,9-dione (462)



m-CPBA (151 mg, 0.66 mmol) was added to a stirring solution of enamide **441** (50.4 mg, 0.022 mmol) and $NaHCO_3$ (92 mg, 1.10 mmol) in CH_2Cl_2 (2.2 mL). The reaction was stirred for 16 h. Sat. aq. Na_2SO_3 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (50% EtOAc/hexane) provided the title compound (47.8 mg, 89%) as a colourless oil; ν_{max} / cm^{-1}: 3440 (br.), 2953 (w), 1746 (s), 1635 (s), 1447 (s), 1266 (s), 1167 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 (2H, m, ArCH), 7.32–7.26 (3H, m, ArCH), 6.12 (1H, dt, *J* = 8.0, 1.0 Hz, C**7**-H), 5.79 (1H, dt, *J* = 8.0, 5.0 Hz, C**6**-H), 5.21 (1H, d, *J* = 14.0 Hz, 1 × C**8**-H_2), 4.58 (1H, dd, *J* = 13.5, 6.0 Hz, 1 × C**5**-H_2), 4.04 (1H, d, *J* = 14.0 Hz, 1 × C**8**-H_2), 3.34 (1H, d, *J* = 13.5 Hz, 1 × C**5**-H_2), 2.89 (1H, m, 1 × C**2**/**3**-H_2), 2.62–2.58 (2H, m, 2 × C**2**/**3**-H_2), 2.49

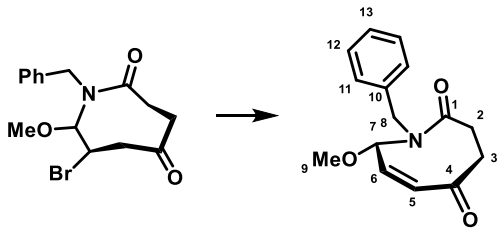
(1H, m, 1 × C**2**/**3**-$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.7 (C**4**), 171.7 (C**1**), 137.2 (C**9**), 132.1 (C**7**), 130.7 (C**6**), 129.3, 128.6 (C**10**, C**11**), 127.9 (C**12**), 60.8 (C**5**), 50.8 (C**8**), 34.5, 32.2 (C**2**, C**3**); HRMS: (ESI^+) Calculated for $C_{14}H_{16}NO_3$: 246.1125. Found $[M + H]^+$: 246.1126.

1-Benzyl-7-bromo-8-methoxyazocane-2,5-dione (464a) ***and*** **2-Benzyl-8-bromo-6-methoxy-9-oxa-2-azabicyclo[4.2.1]nonan-3-one (465)**



Bromine (0.223 mL, 4.36 mmol) was added to a stirring solution of enamide **441** (500 mg, 2.18 mmol) and $NaHCO_3$ (549 mg, 6.54 mmol) in MeOH (11 mL) under an atmosphere of argon. After 30 minutes, sat. aq. Na_2SO_3 (10 mL) was added and the aqueous layer was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. *The products were formed in a 3.3:1 ratio of* ***464a*** *(1:1 d.r.):****465****. Note: It is convenient to proceed to the next step as the diastereomers are inconsequential and the ketal side product cannot be separated at this point*. FCC (25% EtOAc/PhMe) provided the title aminal **464a** and title ketal **465** as an inseparable mixture (737 mg, 100%, 3:1 **464a**:**465**) as a colourless oil. *The relative stereochemistry of the products was not determined*; **Data for the mixture of compounds 464a and 465:** ν_{max} / cm^{-1}: 2944 (w), 1709 (m), 1645 (s), 1453 (m), 1430 (m), 1076 (s); *^{1}H and ^{13}C NMR spectra for diastereomer B of* ***464a*** *was very broad and could not be assigned at this point.* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.26 (10H, m, ArC$\underline{H}$), 5.46 (1H, s, C**7**-$\underline{H}$, C), 4.92 (1H, d, *J* = 15.0 Hz, 1 × C**8**-$\underline{H}_2$, C), 4.69 (1H, d, *J* = 15.0 Hz, 1 × C**8**-$\underline{H}_2$, A), 4.63 (1H, d, *J* = 2.0 Hz, C**7**-$\underline{H}$, A), 4.75 (1H, d, *J* = 15.0 Hz, 1 × C**8**-$\underline{H}_2$, C), 4.35 (1H, br. d, *J* = 15.0 Hz, 1 × C**8**-$\underline{H}_2$, A), 4.25 (1H, m, C**6**-$\underline{H}$, C), 3.96 (1H, br. m, C**6**-$\underline{H}$, A), 3.59 (1H, br. m, 1 × C**5**-$\underline{H}_2$, A), 3.40 (3H, s, C**9**-$\underline{H}_3$, C), 3.16 (3H, s, C**9**-$\underline{H}_3$, A), 2.89 (1H, m, 1 × C**2**-$\underline{H}_2$, C), 2.71-2.55 (5H, m, 2 × C**2**-$\underline{H}_2$, 2 × C**3**-$\underline{H}_2$, 1 × C**5**-$\underline{H}_2$, A), 2.46 (1H, m, 1 × C**2**-$\underline{H}_2$, C), 2.14 (1H, m, 1 × C**3**-$\underline{H}_2$, C), 1.81 (1H, m, 1 × C**3**-$\underline{H}_2$, C); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.2 (C**4**, A), 172.4 (C**1**, A), 172.1 (C**1**, C), 137.2 (C**10**, C), 136.9 (C**10**, A), 129.1, 129.0, 128.8, 128.4, 128.2, 127.8 (C**11**, C**12**, C**13**, A+C), 112.6 (C**4**, C), 95.9 (C**7**, C), 91.3 (C**7**, A), 57.2 (C**9**, A), 51.7 (C**8**, C), 50.9 (C**8**, A), 50.3 (C**9**, C), 48.0 (C**6**, C), 47.7 (C**6**, A), 44.7 (C**2**, C), 44.1 (C**2**/**3**, A), 43.8 (C**5**, A), 42.0 (C**2**/**3**, A), 33.7 (C**2**, C), 33.3 (C**3**, C); HRMS: (ESI^+) Calculated for $C_{15}H_{19}BrNO_3$: 340.0543. Found $[M + H]^+$: 340.0549.

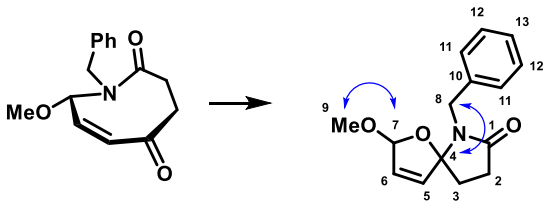
(*Z*)-1-Benzyl-8-methoxy-1,3,4,8-tetrahydroazocine-2,5-dione (467)



464a **467**

General Procedure K: β-Bromoketone **464a** (150 mg, 0.44 mmol, 3:1 **464a**:**465**) and DBU (0.13 mL, 0.88 mmol) were employed. The reaction was quenched after approximately 20 minutes. CH_2Cl_2 (10 mL) was added and the organic layer was washed with 10 wt% aq. citric acid (2 × 5 mL) and sat. aq. $NaHCO_3$ (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* providing the title compound and ketal as a mixture (109 mg, 84%, 1.2:1 aminal:ketal) as a colourless oil. *Note: On a larger scale, aminal **467** was found to degrade rapidly on silica;* ν_{max} / cm^{-1}: 2928 (w), 1654 (s), 1454 (m), 1349 (m), 1074 (m); ^1H NMR (CD_2Cl_2, 400 MHz): δ 7.35–7.23 (5H, m, 2 × C**11**-H, 2 × C**12**-H, C**13**-H), 5.98 (1H, dd, *J* = 13.0, 5.0 Hz, C**6**-H), 5.83 (1H, dd, *J* = 13.0, 1.0 Hz, C**5**-H), 5.02 (1H, dd, *J* = 5.0, 1.0 Hz, C**7**-H), 4.76 (1H, d, *J* = 15.0 Hz, 1 × C**8**-H_2), 4.40 (1H, d, *J* = 15.0 Hz, 1 × C**8**-H_2), 3.43 (1H, m, 1 × C**2**-H_2), 3.19 (3H, s, C**9**-H_2), 2.90 (1H, m, 1 × C**3**-H_2), 2.78–2.66 (2H, m, 1 × C**2**-H_2, 1 × C**3**-H_2); ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 203.7 (C**4**), 174.0 (C**1**), 137.2 (C**10**), 134.2 (C**6**), 129.1 (ArC), 129.0 (C**5**), 128.7 (ArC), 127.9 (C**13**), 87.9 (C**7**), 57.1 (C**9**), 50.4 (C**8**), 43.6 (C**3**), 31.0 (C**2**); HRMS: (ESI^+) Calculated for $C_{15}H_{17}NNaO_3$: 282.1101. Found $[M + Na]^+$: 282.1112.

6-Benzyl-2-methoxy-1-oxa-6-azaspiro[4.4]non-3-en-7-one (468)

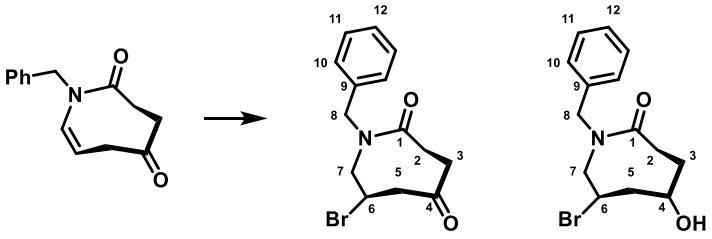


467 **468**

$BF_3{\cdot}Et_2O$ (0.096 mL, 0.77 mmol) was added to a stirring solution of aminal **467** (100 mg, 0.39 mmol) and triethylsilane (0.06 mL, 0.386 mmol) in CH_2Cl_2 (3.8 mL) at -78 °C. TLC indicated consumption of aminal after 15 minutes. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (40% EtOAc/hexane) provided the title compound (16 mg, 16%, 2:1 d.r., A:B) as a colourless oil. *The relative stereochemistry of product diastereomers was not determined*; **Data for the mixture of diastereomers A and B:** ν_{max} / cm^{-1}: 2929 (w), 1697 (s), 1396 (m), 1192 (m), 1019 (s); ^1H NMR (CD_2Cl_2, 400 MHz): δ 7.17–6.99 (10H, m, 5 × ArC**H**, A+B), 5.75

(1H, dd, *J* = 6.0, 1.0 Hz, C**5**-H, B), 5.71 (1H, dd, *J* = 6.0, 1.0 Hz, C**5**-H, A), 5.55 (1H, dd, *J* = 6.0, 1.0 Hz, C**6**-H, B), 5.43 (1H, m, C**6**-H, A), 5.30 (1H, dd, *J* = 1.0, 1.0 Hz, C**7**-H, A), 5.13 (1H, dd, *J* = 1.0, 1.0 Hz, C**7**-H, B), 4.43 (1H, d, *J* = 16.0 Hz, 1 × C**8**-H_2, A), 4.26 (1H, d, *J* = 15.5 Hz, 1 × C**8**-H_2, B), 3.92 (1H, d, *J* = 16.0 Hz, 1 × C**8**-H_2, A), 3.82 (1H, d, *J* = 15.5 Hz, C**8**-H_2, B), 3.21 (3H, s, C**9**-H_3, A), 3.15 (3H, s, C**9**-H_3, B), 2.48–2.38 (2H, m, 1 × C**2**-H_2, A+B), 2.27–2.18 (2H, m, 1 × C**2**-H_2, A+B), 2.12–1.93 (4H, m, 2 × C**3**-H_2, A+B); ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 175.0 (C**1**, B), 174.8 (C**1**, A), 138.9 (C**10**, A), 138.4 (C**10**, B), 134.4 (C**6**, B), 133.8 (C**6**, A), 130.8 (C**5**, B), 130.3 (C**5**, A), 128.2, 128.1, 127.9, 127.8, 126.9, 126.7 (C**11**, C**12**, C**13**, A+B), 107.7 (C**7**, B), 107.3 (C**7**, A), (C**4**, B), 104.4 (C**4**, A), 56.0 (C**9**, A), 54.5 (C**9**, B), 42.6 (C**8**, B), 42.0 (C**8**, A), 32.5 (C**3**, B), 31.6 (C**3**, A), 28.8 (C**2**, B), 28.8 (C**2**, A); *The structure was assigned based on HMBC correlation between C**8** and C**4** as well as C**9** and C**7**, shown in blue*. HRMS: (ESI$^+$) Calculated for $C_{15}H_{17}NNaO_3$: 282.1101. Found $[M + Na]^+$: 282.1104.

1-Benzyl-7-bromoazocane-2,5-dione (471) *and* 1-Benzyl-7-bromo-5-hydroxyazocan-2-one (472)

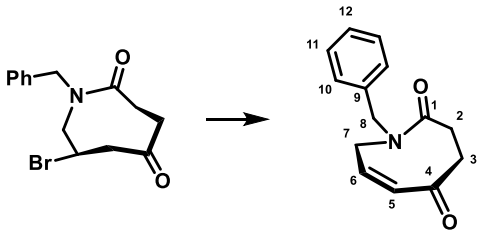


441 471 472

General Procedure J: Enamide **441** (170 mg, 0.74 mmol) was employed. FCC (60–90% EtOAc/hexane) provided ketone (106 mg, 46%) as a colourless oil and the alcohol (88 mg, 38%) as a yellow foam; **Data for ketone 471:** ν_{max} / cm^{-1}: 2963 (w), 1706 (s), 1642 (s), 1452 (m), 1417 (m), 1102 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.29 (3H, m, ArCH), 7.23 (2H, m, ArCH), 4.64–4.55 (2H, m, 2 × C**8**-H_2), 3.92 (1H, m, C**6**-H), 3.87 (1H, dd, *J* = 15.0, 10.0 Hz, 1 × C**7**-H_2), 3.64 (1H, dd, *J* = 15.0, 2.0 Hz, 1 × C**7**-H_2), 3.20 (1H, m, 1 × C**2**-H_2), 3.15 (1H, dd, *J* = 12.0, 11.0 Hz, 1 × C**5**-H_2), 2.95 (1H, dd, *J* = 12.0, 4.0 Hz, 1 × C**5**-H_2), 2.80–2.72 (2H, m, 2 × C**3**-H_2), 2.62 (1H, dt, *J* = 13.5, 5.0 Hz, 1 × C**2**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.1 (C**4**), 172.3 (C**1**), 136.5 (C**9**), 129.0, 128.6 (C**10**, C**11**), 128.2 (C**12**), 55.4 (C**7**), 50.4 (C**8**), 49.4 (C**5**), 44.2 (C**6**), 44.0 (C**3**), 29.4 (C**2**); HRMS: (ESI$^+$) Calculated for $C_{14}H_{16}BrNO_2$: 310.0437. Found $[M + H]^+$: 310.0438. **Data for alcohol 472:** *The relative stereochemistry of product **472** was not determined*; ν_{max} / cm^{-1}: 3358 (br.), 2403 (w), 2254 (w), 1626 (s), 1452 (m), 1101 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.26 (5H, m, ArCH), 4.73 (1H, d, *J* = 14.5 Hz, C**8**-H_2), 4.55 (1H, d, *J* = 14.5 Hz, C**8**-H_2), 4.16–4.05 (2H, m, C**4**-H, C**6**-H), 3.72 (1H, dd, *J* = 15.5, 10.5 Hz, C**7**-H_2), 3.61 (1H, dd, *J* = 15.5, 5.0 Hz, C**7**-H_2), 2.70–2.58 (2H, m, 2 × C**2**-H_2), 2.26–2.11 (2H, m, 1 × C**3**-H_2, 2 × C**5**-H_2), 1.95 (1H, m, C**3**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.3 (C**1**), 137.2 (C**9**), 128.9, 128.4 (C**10**, C**11**), 128.0 (C**12**), 68.0 (C**4**), 53.0 (C**7**), 49.3 (C**8**), 47.5 (C**6**), 42.5 (C**5**),

36.7 (C**3**), 31.1 (C**2**); HRMS: (ESI$^+$) Calculated for $C_{14}H_{19}BrNO_2$: 312.0594. Found [M + H]$^+$: 312.0596.

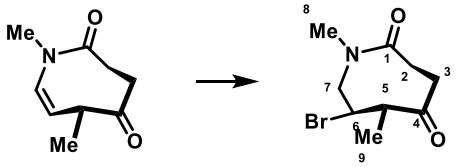
(*Z*)-1-Benzyl-1,3,4,8-tetrahydroazocine-2,5-dione (473)



471 **473**

General Procedure K: Bromoketone **471** (106 mg, 0.34 mmol) and NEt_3 (0.24 mL, 1.71 mmol) were employed. The reaction was quenched after approximately 3 h. FCC (80% EtOAc/hexane) provided the title compound (63 mg, 81%) as a colourless oil; ν_{max} / cm^{-1}: 2923 (w), 1681 (s), 1648 (s), 1454 (m), 1416 (m), 1176 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.24 (3H, m, ArC<u>H</u>), 7.21 (2H, m, ArC<u>H</u>), 6.00–5.93 (2H, m, C**5**-<u>H</u>, C**6**-<u>H</u>), 4.54 (2H, s, C**8**-<u>H</u>$_2$), 3.95 (2H, d, *J* = 2.5 Hz, C**7**-<u>H</u>$_2$), 2.95 (2H, m, C**3**-<u>H</u>$_2$), 2.87 (2H, m, C**2**-<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.7 (C**4**), 174.0 (C**1**), 136.7 (C**9**), 134.3 (C**5**), 130.6 (C**6**), 128.8, 128.5 (C**10**, C**11**), 127.9 (C**12**), 51.2 (C**8**), 48.5 (C**7**), 44.8 (C**3**), 30.0 (C**2**); HRMS: (ESI$^+$) Calculated for $C_{14}H_{16}NO_2$: 230.1176. Found [M + H]$^+$: 230.1183.

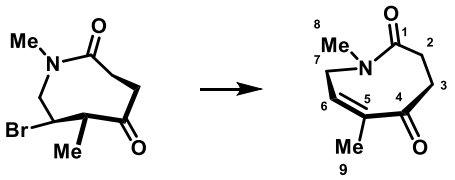
7-Bromo-1,6-dimethylazocane-2,5-dione (474a)



403a **474a**

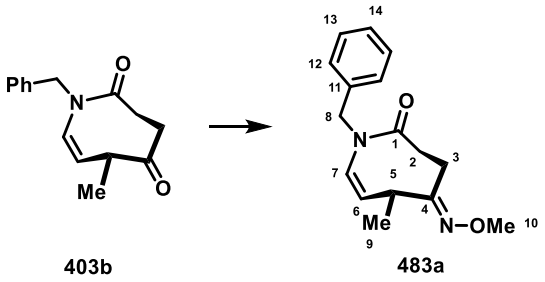
General Procedure J: Enamide **403a** (167 mg, 1.00 mmol) was employed. FCC (80% EtOAc/hexane) provided ketone (161 mg, 65%) as a colourless oil. *The relative stereochemistry of product **474a** was not determined*; ν_{max} / cm^{-1}: 2935 (w), 1709 (s), 1633 (s), 1470 (m), 1401 (m), 1104 (m); *The ^{1}H and ^{13}C NMR spectra of the product are broad in both $CDCl_3$ and MeOD-d_3. As a result, the signals for C**8** could not be identified. The proposed structure was confirmed upon E1cB elimination of the bromide.* ^{1}H NMR (CD_3OD, 400 MHz): δ 4.16 (1H, br. m, C**7**-<u>H</u>$_2$), 4.03 (1H, ddd, *J* = 12.0, 9.0, 3.0 Hz, C**6**-<u>H</u>), 3.78 (1H, br. d, *J* = 16.0 Hz, C**7**-<u>H</u>$_2$), 3.21 (1H, m, C**5**-<u>H</u>), 2.98–2.88 (2H, m, C**3**-<u>H</u>$_2$), 2.46 (2H, m, C**2**-<u>H</u>$_2$), 1.28 (3H, d, *J* = 6.5 Hz, C**9**-<u>H</u>$_3$); ^{13}C NMR (CD_3OD, 100 MHz): δ 211.3 (C**4**), 173.9 (C**1**), 57.7 (C**7**), 53.4 (C**6**), 50.3 (C**5**), 43.0, 43.0 (C**2**, C**3**), 17.5 (C**9**); HRMS: (ESI$^+$) Calculated for $C_9H_{15}BrNO_2$: 248.0281. Found [M + H]$^+$: 248.0290.

(*Z*)-1,6-Dimethyl-1,3,4,8-tetrahydroazocine-2,5-dione (439a)



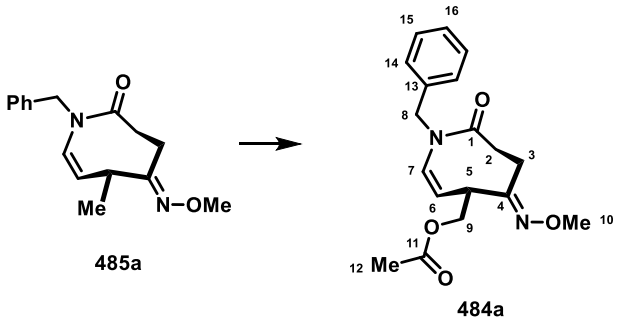
General Procedure K: Bromoketone **474a** (50.0 mg, 0.20 mmol) and DBU (0.06 mL, 0.40 mmol) were employed. The reaction was quenched after approximately 30 minutes. FCC (100% EtOAc) provided the title compound (22.0 mg, 66%) as a colourless oil; ν_{max} / cm^{-1}: 2922 (w), 1684 (s), 1629 (s), 1452 (m), 1400 (m), 1254 (w), 1085 (m); ^{1}H NMR (CD_3OD, 400 MHz): δ 5.97 (1H, m, C**6**-H), 4.10 (2H, m, C**7**-H_2), 2.88–2.80 (7H, m, C**2**-H_2, C**3**-H_2, C**8**-H_3), 1.86 (3H, m, C**9**-H_3); ^{13}C NMR (CD_3OD, 100 MHz): δ 209.0 (C**4**), 175.9 (C**1**), 140.8 (C**5**), 128.6 (C**6**), 50.9 (C**7**), 43.6 (C**3**), 35.7 (C**8**), 31.6 (C**2**), 20.8 (C**9**); HRMS: (ESI^+) Calculated for $C_9H_{14}NO_2$: 168.1019. Found $[M + H]^+$: 168.1027.

(5*E*,7*Z*)-1-Benzyl-5-(methoxyimino)-6-methyl-3,4,5,6-tetrahydroazocin-2(1*H*)-one (483a)



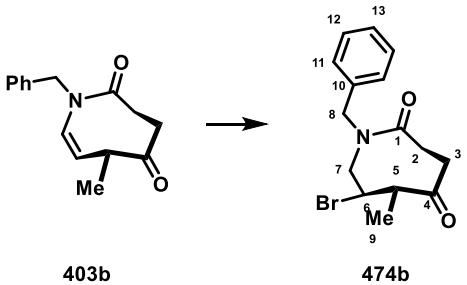
General Procedure L: Ketone **403b** (200 mg, 0.82 mmol), methoxyamine hydrochloride (103 mg, 1.23 mmol) and NaOAc (101 mg, 1.23 mmol) were employed. The reaction was carried out at room temperature for 1 h. The title compound (231 mg, 104%, 3:1 d.r., A+B) was afforded as a colourless oil. *The oxime diastereomers were not separated at this stage*; ν_{max} / cm^{-1}: 2933 (w), 1647 (s), 1442 (m), 1391 (m), 1047 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.23 (5H, m, ArC**H**), 5.98 (1H, dd, *J* = 7.5, 1.0 Hz, C**7**-H), 5.17 (1H, dd, *J* = 8.5, 7.5 Hz, C**6**-H), 5.01 (1H, d, *J* = 14.0 Hz, 1 × C**8**-H_2), 4.25 (1H, d, *J* = 14.0 Hz, 1 × C**8**-H_2), 3.80 (3H, s, C**10**-H_3), 3.32 (1H, ddd, *J* = 16.0, 7.0, 2.5 Hz, 1 × C**3**-H_2), 2.68–2.49 (3H, m, 2 × C**2**-H_2, C**5**-H), 2.17 (1H, ddd, *J* = 16.0, 13.0, 3.5 Hz, 1 × C**3**-H_2), 0.96 (3H, d, *J* = 7.0 Hz, C**9**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.8 (C**1**), 157.4 (C**4**), 136.6 (C**11**), 130.0 (C**6**), 128.9, 128.6 (C**12**, C**13**), 128.2 (C**7**), 127.7 (C**14**), 61.5 (C**10**), 50.0 (C**8**), 36.5 (C**5**), 32.5 (C**2**), 22.9 (C**3**), 16.9 (C**9**); HRMS: (ESI^+) Calculated for $C_{16}H_{21}N_2O_2$: 273.1598. Found $[M + H]^+$: 273.1599.

((2*Z*,5*E*)-1-Benzyl-5-(methoxyimino)-8-oxo-1,4,5,6,7,8-hexahydroazocin-4-yl)methyl acetate (484a)



General Procedure N: Oxime **485a** (100 mg, 0.37 mmol), $Pd(OAc)_2$ (8.30 mg, 0.037 mmol) and $PhI(OAc)_2$ (131 mg, 0.41 mmol) were employed in AcOH:Ac_2O (3.7 mL, 1:1). The reaction was heated at 80 °C for 16 h. FCC (60% EtOAc/hexane) provided the title compound (54 mg, 45%, >15:1 d.r.) as a yellow oil and oxime (29 mg, 29%); ν_{max} / cm^{-1}: 3360 (br.), 2937 (w), 1738 (m), 1649 (s), 1440 (m), 1231 (s), 1043 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.22 (5H, m, ArC<u>H</u>), 6.12 (1H, dd, *J* = 7.5, 1.0 Hz, C**7**-<u>H</u>), 5.23 (1H, dd, *J* = 8.5, 7.5 Hz, C**6**-<u>H</u>), 5.02 (1H, d, *J* = 14.5 Hz, 1 × C**8**-<u>H_2</u>), 4.27 (1H, d, *J* = 14.5 Hz, 1 × C**8**-<u>H_2</u>), 4.22–4.19 (2H, m, 2 × C**9**-<u>H_2</u>), 3.79 (3H, s, C**10**-<u>H_3</u>), 3.42 (1H, ddd, *J* = 16.5, 6.0, 3.5 Hz, 1 × C**3**-<u>H_2</u>), 2.97 (1H, q, *J* = 7.5 Hz, C**5**-<u>H</u>), 2.61–2.53 (2H, m, 2 × C**2**-<u>H_2</u>), 2.14 (1H, m, 1 × C**3**-<u>H_2</u>), 1.85 (3H, s, C**12**-<u>H_3</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6 (C**1**), 170.9 (C**11**), 154.2 (C**4**), 136.8 (C**13**), 130.9 (C**7**), 128.8, 128.7 (C**14**, C**15**), 127.8 (C**16**), 125.2 (C**6**), 64.1 (C**9**), 61.8 (C**10**), 50.6 (C**8**), 41.3 (C**5**), 32.5 (C**2**), 22.8 (C**3**), 21.0 (C**12**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{23}N_2O_4$: 331.1652. Found $[M + H]^+$: 331.1630.

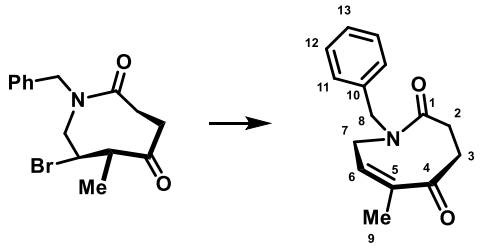
1-Benzyl-7-bromo-6-methylazocane-2,5-dione (474b)



General Procedure J: Enamide **403b** (1.00 g, 4.11 mmol) was employed. FCC (50–60–90% EtOAc/hexane) provided ketone (895 mg, 67%) as a colourless oil. *The relative stereochemistry of the product was not determined*; ν_{max} / cm^{-1}: 3301 (br.), 2970 (w), 2933 (w), 1710 (s), 1645 (s), 1453 (s), 1418 (m), 1120 (m); ^{1}H NMR (CD_3OD, 400 MHz): δ 7.37–7.27 (3H, m, ArC<u>H</u>), 7.23 (2H, m, ArC<u>H</u>), 4.66 (1H, d, *J* = 15.0 Hz, 1 × C**8**-<u>H_2</u>), 4.40 (1H, br. m, 1 × C**8**-<u>H_2</u>), 4.14 (1H, dd, *J* = 16.0, 10.5 Hz, 1 × C**7**-<u>H_2</u>), 3.77 (1H, m, C**6**-<u>H</u>), 3.65 (1H, dd, *J* = 16.0, 3.0 Hz, 1 × C**7**-<u>H_2</u>), 3.53 (1H, m, 1 × C**2**-<u>H_2</u>), 3.26 (1H, qd, *J* = 6.5, 4.5 Hz, C**5**-<u>H</u>), 2.97 (1H, m, 1 × C**3**-<u>H_2</u>), 2.56–2.47 (2H, m, 1 × C**2**-<u>H_2</u>, 1 × C**3**-<u>H_2</u>),

1.23 (3H, d, *J* = 6.5 Hz, C**9**-H$_3$); ^{13}C NMR (CD_3OD, 100 MHz): δ 212.1 (C**4**), 175.4 (C**1**), 137.8 (C**10**), 129.7, 129.5, 128.8 (ArC), 56.4 (C**7**), 55.2 (C**6**), 51.7 (C**5**), 50.8 (C**8**), 44.4 (C**3**), 29.6 (C**2**), 19.4 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{18}BrNNaO_2$: 346.0413. Found [M + Na]$^+$: 346.0409.

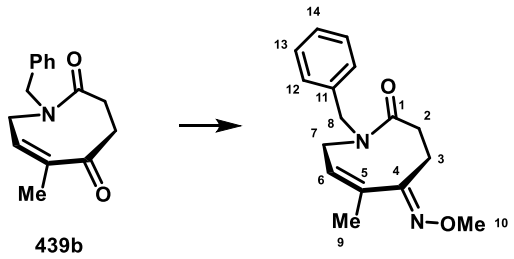
(*Z*)-1-Benzyl-6-methyl-1,3,4,8-tetrahydroazocine-2,5-dione (439b)



474b **439b**

General Procedure K: Bromoketone **474b** (60.0 mg, 0.190 mmol) and DBU (0.100 mL, 0.756 mmol) were employed. The reaction was quenched after approximately 30 minutes. FCC (60% EtOAc/hexane) provided the title compound (31.0 mg, 67%) as a colourless oil; ν_{max} / cm^{-1}: 3316 (br.), 2919 (w), 1686 (s), 1638 (s), 1453 (s), 1418 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27–7.14 (5H, m, ArC<u>H</u>), 5.59 (1H, m, C**6**-<u>H</u>), 4.44 (2H, s, C**8**-<u>H</u>$_2$), 3.75 (2H, m, C**7**-<u>H</u>$_2$), 2.82–2.78 (4H, m, C**2**-H$_2$, C**3**-<u>H</u>$_2$), 1.76 (3H, m, C**9**-<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.1 (C**4**), 173.3 (C**1**), 140.1 (C**5**), 136.9 (C**10**), 128.7, 128.4 (C**11**, C**12**), 127.7 (C**13**), 126.4 (C**6**), 50.7 (C**8**), 46.9(C**7**), 42.8 (C**3**), 31.1 (C**2**), 20.9 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{18}NO_2$: 244.1332. Found [M + H]$^+$: 244.1330.

(5*E*,6*Z*)-1-Benzyl-5-(methoxyimino)-6-methyl-3,4,5,8-tetrahydroazocin-2(1*H*)-one (485)

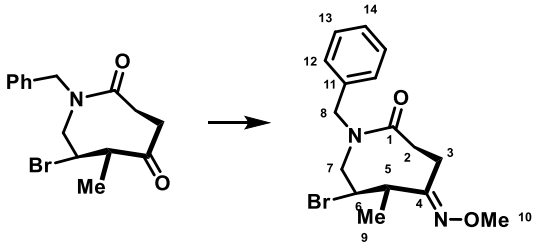


439b **485**

General Procedure L: Ketone **439b** (81.0 mg, 0.33 mmol), methoxyamine hydrochloride (42.0 mg, 0.50 mmol) and NaOAc (41.0 mg, 0.50 mmol) were employed. The reaction was carried out at room temperature for 6 h. The title compound (91 mg, 100%, 2:1 d.r., A+B) was afforded as a pale yellow oil; ν_{max} / cm^{-1}: 2936 (w), 1633 (s), 1453 (m), 1421 (m), 1045 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.22 (10H, m, ArC<u>H</u>, A+B), 5.66 (1H, tq, *J* = 7.5, 1.5 Hz, C**6**-<u>H</u>, A), 5.45 (1H, br. m, C**6**-<u>H</u>, B), 4.54 (2H, s, C**8**-<u>H</u>$_2$, A), 3.90 (3H, s, C**10**-<u>H</u>$_3$, A), 3.84 (3H, s, C**10**-<u>H</u>$_3$, B), 3.73 (2H, d, *J* = 7.5 Hz, C**7**-<u>H</u>$_2$, A), 3.68 (2H, br. m, C**7**-<u>H</u>$_2$, B), 2.86 (2H, m, C**2**-<u>H</u>$_2$, A), 2.76 (2H, m, C**3**-<u>H</u>$_2$, A), 1.88 (3H, s, C**9**-<u>H</u>$_3$, A), 1.84 (3H, s, C**9**-<u>H</u>$_3$, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0 (C**1**, A), 158.6 (C**4**, A), 140.2 (C**5**, A), 137.5 (C**11**, A), 137.5 (C**11**, B), 128.7, 128.4 (C**12** (A), C**13** (A)), 128.3 (C**12**/**13**, B), 127.6 (C**14**,

A), 125.0 (C**6**, A), 62.0 (C**10**, A), 49.8 (C**8**, A), 45.1 (C**7**, A), 33.4 (C**2**, A), 25.1 (C**3**, A), 22.6 (C**9**, A); HRMS: (ESI$^+$) Calculated for $C_{16}H_{20}N_2NaO_2$: 295.1417. Found [M + Na]$^+$: 295.1429.

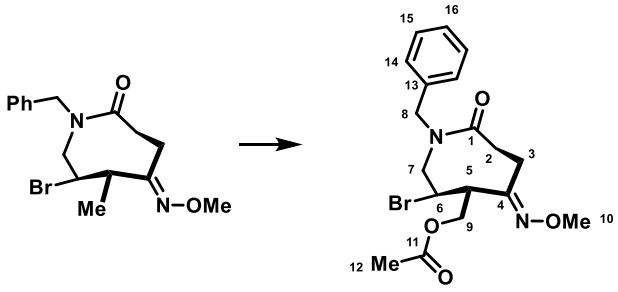
(*E*)-1-Benzyl-7-bromo-5-(methoxyimino)-6-methylazocan-2-one (487a)



474b 487a

General Procedure L: Ketone **474b** (162 mg, 0.50 mmol), methoxyamine hydrochloride (63.0 mg, 0.75 mmol) and NaOAc (62.0 mg, 0.75 mmol) were employed. The reaction was carried out at room temperature for 16 h. The title compound (158 mg, 89%, >15:1 d.r.) was afforded as a colourless oil; ν_{max} / cm^{-1}: 2936 (w), 1644 (s), 1452 (s), 1412 (m), 1164 (m), 1045 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.24 (5H, m, ArC**H**), 5.05 (1H, br., C**8**-H$_2$), 4.74 (1H, d, *J* = 14.5, C**8**-H$_2$), 3.97 (1H, m, C**6**-H), 3.86–3.79 (4H, m, 1 × C**7**-H$_2$, 3 × C**10**-H$_3$), 3.71 (1H, dd, *J* = 16.5, 5.5 Hz, C**7**-H$_2$), 3.47 (1H, m, C**2**-H$_2$), 2.80 (1H, m, C**3**-H$_2$), 2.68–2.54 (2H, m, 1 × C**3**-H$_2$, C**5**-H), 2.01 (1H, m, C**2**-H$_2$), 1.40 (3H, d, *J* = 7.0 Hz, C**9**-H$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.5 (C**1**), 160.9 (C**4**), 137.1 (C**11**), 128.8, 128.6 (C**12**, C**13**), 127.7 (C**14**), 61.9 (C**7**), 61.6 (C**10**), 57.7 (C**6**), 49.7 (C**8**), 44.8 (C**5**), 31.8 (C**3**), 27.0 (C**2**), 20.0 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{16}H_{22}BrN_2O_2$: 353.0859. Found [M + H]$^+$: 353.0869.

(*E*)-(1-Benzyl-3-bromo-5-(methoxyimino)-8-oxoazocan-4-yl)methyl acetate (488a)

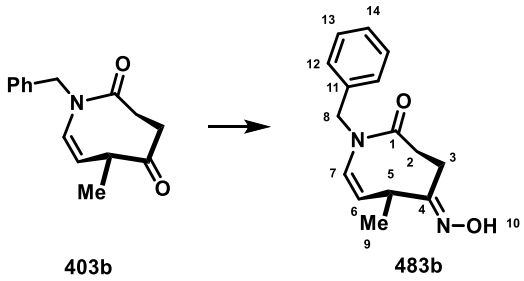


487a 488a

General Procedure N: Oxime **487a** (80.0 mg, 0.226 mmol), $Pd(OAc)_2$ (5.10 mg, 0.0230 mmol) and $PhI(OAc)_2$ (109 mg, 0.340 mmol) were employed in AcOH:Ac_2O (2.3 mL, 1:1). The reaction was heated at 100 °C for 3 h. FCC (60% EtOAc/hexane) provided the title compound (37.0 mg, 40%, >15:1 d.r.) as an orange oil; ν_{max} / cm^{-1}: 2936 (w), 1739 (s), 1637 (s), 1453 (s), 1226 (s), 1045 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.24 (5H, m, ArC**H**), 5.05 (1H, br. m, C**8**-H$_2$), 4.75–4.63 (2H, m, 1 × C**8**-H$_2$, 1 × C**9**-H$_2$), 4.34 (1H, dd, *J* = 10.0, 10.0 Hz, C**9**-H$_2$), 3.98 (1H, m, C**6**-H), 3.86–3.72 (5H, m, 2 × C**7**-H$_2$, C**10**-H$_3$), 3.53 (1H, m, C**2**-H$_2$), 2.93 (1H, m, C**5**-H), 2.81 (1H, m, C**3**-H$_2$), 2.58 (1H, m, C**3**-H$_2$), 2.08–

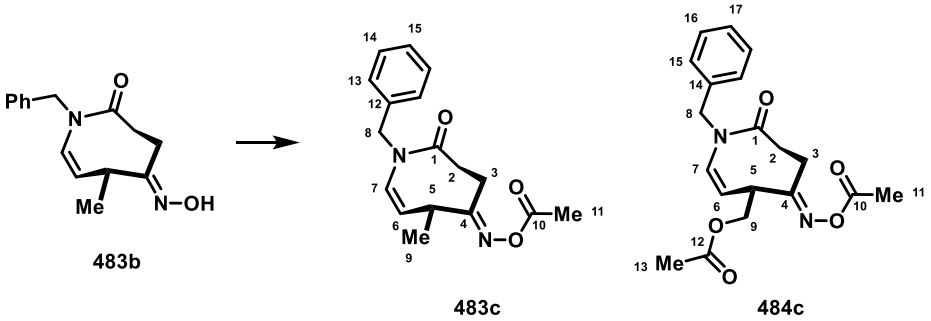
1.98 (4H, m, 1 × C**2**-H$_2$, C**12**-H$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3 (C**1**), 170.7 (C**11**), 157.0 (C**4**), 136.9 (C**13**), 128.8, 128.6 (C**14**, C**15**), 127.8 (C**16**), 67.3 (C**9**), 62.2 (C**10**), 49.9 (C**8**), 49.1 (C**5**), 31.9 (C**3**), 27.2 (C**2**), 21.0 (C**12**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{23}BrN_2NaO_4$: 433.0733. Found [M + Na]$^+$: 433.0720.

(5*E*,7*Z*)-1-Benzyl-5-(hydroxyimino)-6-methyl-3,4,5,6-tetrahydroazocin-2(1*H*)-one (483b)



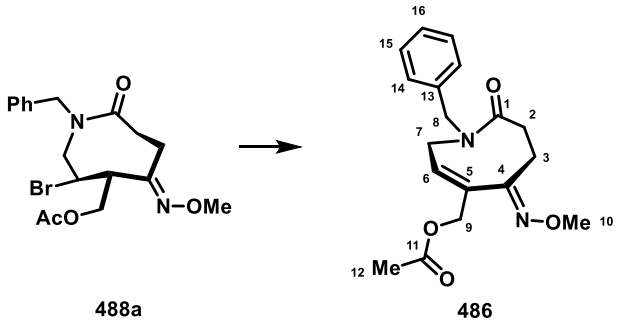
General Procedure L: Ketone **403b** (444 mg, 1.72 mmol), hydroxylamine hydrochloride (191 mg, 2.75 mmol) and NaOAc (222 mg, 2.75 mmol) were employed. The reaction was carried out at room temperature for 4 h. The title compound (450 mg, 96%, 3:1 d.r.) was afforded as a colourless oil. *The oxime diastereomers were separated by FCC (50% EtOAc/hexane) for analysis*; **Data for the first diastereomer (A) to elute by FCC:** ν_{max} / cm^{-1}: 3253 (br.), 2970 (w), 1620 (s), 1445 (s), 1389 (m), 1186 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (1H, br. s, OH), 7.34–7.23 (5H, m, ArCH), 6.01 (1H, dd, *J* = 7.5, 1.0 Hz, C**7**-H), 5.16 (1H, dd, *J* = 8.5, 7.5 Hz, C**6**-H), 5.02 (1H, d, *J* = 14.0 Hz, 1 × C**8**-H$_2$), 4.25 (1H, d, *J* = 14.0 Hz, 1 × C**8**-H$_2$), 2.68 (1H, m, C**5**-H), 2.64–2.54 (2H, m, C**3**-H$_2$), 2.18 (1H, ddd, *J* = 16.0, 12.0, 4.0 Hz, 1 × C**2**-H$_2$), 0.94 (3H, d, *J* = 6.5 Hz, C**9**-H$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7 (C**1**), 158.7 (C**4**), 136.6 (C**10**), 129.7 (C**6**), 129.0, 128.6 (C**11**, C**12**), 128.6 (C**7**), 127.8 (C**13**), 50.0 (C**8**), 36.5 (C**5**), 32.4 (C**2**), 22.4 (C**3**), 16.8 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{19}N_2O_2$: 259.1441. Found [M + H]$^+$: 259.1443; **Data for the second diastereomer (B) to elute by FCC:** ν_{max} / cm^{-1}: 3253 (br.), 1625 (s), 1445 (s), 1389 (s), 1183 (m), 939 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (1H, br. s, OH), 7.31–7.22 (5H, m, ArCH), 5.81 (1H, dd, *J* = 8.5, 2.0 Hz, C**7**-H), 5.33 (1H, dd, *J* = 8.5, 5.5 Hz, C**6**-H), 4.96 (1H, d, *J* = 14.5 Hz, 1 × C**8**-H$_2$), 4.28 (1H, d, *J* = 14.5 Hz, 1 × C**8**-H$_2$), 3.85 (1H, m, C**5**-H), 2.89 (1H, m, 1 × C**2**-H$_2$), 2.63–2.48 (3H, m, 1 × C**2**-H$_2$, 2 × C**3**-H$_2$), 1.13 (3H, d, *J* = 7.5 Hz, C**9**-H$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0 (C**1**), 159.4 (C**4**), 136.8 (C**10**), 128.9, 128.5 (C**11**, C**12**), 127.9 (C**7**), 127.5 (C**13**), 126.9 (C**6**), 50.5 (C**8**), 32.7 (C**3**), 30.9 (C**5**), 28.7 (C**2**), 17.1 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{19}N_2O_2$: 259.1441. Found [M + H]$^+$: 259.1447.

(5*E*,7*Z*)-5-(Acetoxyimino)-1-benzyl-6-methyl-3,4,5,6-tetrahydroazocin-2(1*H*)-one (483c) ***and*** **((2*Z*,5*E*)-5-(Acetoxyimino)-1-benzyl-8-oxo-1,4,5,6,7,8-hexahydroazocin-4-yl)methyl acetate (484c)**



General Procedure N: Oxime **483b** (250 mg, 0.194 mmol), $Pd(OAc)_2$ (4.3 mg, 0.019 mmol) and $PhI(OAc)_2$ (93.5 mg, 0.290 mmol) were employed in AcOH:Ac_2O (1.93 mL, 1:1). The reaction was heated at 100 °C for 6 h. FCC (40% EtOAc/hexane) provided acetyl oxime **483c** (27 mg, 46%) as a yellow oil and oxidised product **484c** as a mixture with both non-oxidised diastereomers (16 mg, 2:1.5:1, 10%) as a yellow oil; **Data for acetyl oxime 483c:** ν_{max} / cm^{-1}: 2930 (w), 1765 (s), 1740 (s), 1647 (s), 1365 (m), 1201 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.22 (5H, m, ArC<u>H</u>), 6.04 (1H, d, *J* = 7.5 Hz, C**7**-<u>H</u>), 5.20 (1H, dd, *J* = 8.5, 7.5 Hz, C**6**-<u>H</u>), 5.01 (1H, d, *J* = 14.0 Hz, 1 × C**8**-<u>H_2</u>), 4.20 (1H, d, *J* = 14.0 Hz, 1 × C**8**-<u>H_2</u>), 3.29 (1H, m, 1 × C**3**-<u>H_2</u>), 2.78 (1H, m, C**5**-<u>H</u>), 2.67–2.52 (2H, m, 2 × C**2**-<u>H_2</u>), 2.35 (1H, m, 1 × C**3**-<u>H_2</u>), 2.12 (3H, s, C**11**-<u>H_3</u>), 1.02 (3H, d, *J* = 7.0 Hz, C**9**-<u>H_3</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.9 (C**1**), 168.8 (C**10**), 166.0 (C**4**), 136.3 (C**12**), 129.2 (C**7**), 128.9, 128.6 (C**13**, C**14**), 128.6 (C**6**), 127.9 (C**15**), 50.0 (C**8**), 37.2 (C**5**), 32.1 (C**2**), 24.6 (C**3**), 19.9 (C**11**), 16.7 (C**9**); HRMS: (ESI^+) Calculated for $C_{17}H_{20}N_2NaO3$: 323.1366. Found $[M + Na]^+$: 323.1365; **Data for the C-H acetoxylated product 484c:** ν_{max} / cm^{-1}: 2934 (w), 1764 (s), 1747 (s), 1648 (s), 1366 (m), 1204 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.25 (5H, m, ArC<u>H</u>), 6.19 (1H, dd, *J* = 7.5, 1.0 Hz, C**7**-<u>H</u>), 5.29 (1H, dd, *J* = 8.5, 7.5 Hz, C**6**-<u>H</u>), 5.01 (1H, d, *J* = 14.5 Hz, 1 × C**8**-<u>H_2</u>), 4.32 (1H, dd, *J* = 11.0, 6.0 Hz, 1 × C**9**-<u>H_2</u>), 4.29 (1H, dd, *J* = 14.5 Hz, 1 × C**8**-<u>H_2</u>), 4.22 (1H, dd, *J* = 11.0, 8.0 Hz, 1 × C**9**-<u>H_2</u>), 3.41 (1H, ddd, *J* = 15.5, 6.0 3.5 Hz, 1 × C**3**-<u>H_2</u>), 3.15 (1H, m, C**5**-<u>H</u>), 2.65–2.62 (2H, m, 2 × C**2**-<u>H_2</u>), 2.40 (1H, m, 1 × C**3**-<u>H_2</u>), 2.16 (3H, s, C**11**-<u>H_3</u>), 1.86 (3H, s, C**13**-<u>H_3</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.8 (C**1**), 170.6 (C**12**), 168.7 (C**10**), 163.0 (C**4**), 136.4 (C**14**), 131.8 (C**7**), 128.8, 128.8 (C**15**, C**16**), 127.9 (C**17**), 123.4 (C**6**), 63.3 (C**9**), 50.6 (C**8**), 42.1 (C**5**), 32.2 (C**2**), 24.7 (C**3**), 20.9 (C**13**), 20.0 (C**11**); HRMS: (ESI^+) Calculated for $C_{19}H_{22}N_2NaO_5$: 381.1421. Found $[M + Na]^+$: 381.1425.

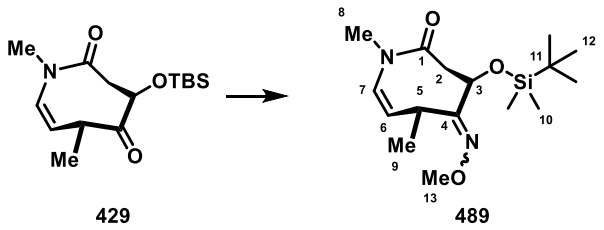
((3*E*,5*E*)-1-Benzyl-5-(methoxyimino)-8-oxo-1,2,5,6,7,8-hexahydroazocin-4-yl)methyl acetate (486)



488a 486

General Procedure K: Bromoketone **488a** (50.1 mg, 0.122 mmol) and DBU (0.091 mL, 0.608 mmol) were employed. The reaction was quenched after approximately 16 h. FCC (80% EtOAc/hexane) provided the title compound (21 mg, 52%) as a pale yellow; ν_{max} / cm^{-1}: 2936 (w), 1739 (s), 1638 (s), 1453 (m), 1421 (m), 1226 (s), 1045 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.23 (5H, m, ArC<u>H</u>), 5.83 (1H, tt, *J* = 6.5, 2.5 Hz, C**6**-<u>H</u>), 4.65 (2H, s, C**9**-<u>H_2</u>), 4.55 (2H, s, C**8**-<u>H_2</u>), 3.90 (3H, s, C**10**-<u>H_3</u>), 3.85–3.81 (2H, m, C**7**-<u>H_2</u>), 2.86–2.81 (4H, m, C**2**-<u>H_2</u>, C**3**-<u>H_2</u>), 2.06 (3H, s, C**12**-<u>H_3</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.0 (C**1**), 170.5 (C**11**), 155.3 (C**4**), 137.6 (C**5**), 137.4 (C**13**), 128.7, 128.5 (C**14**, C**15**), 127.7 (C**16**), 127.4 (C**6**), 66.1 (C**9**), 62.3 (C**10**), 50.2 (C**8**), 45.2 (C**7**), 32.9 (C**2**), 25.8 (C**3**), 21.0 (C**12**); HRMS: (ESI^+) Calculated for $C_{18}H_{22}N_2NaO_4$: 353.1472. Found $[M + Na]^+$: 353.1487.

(5*E*,7*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-(methoxyimino)-1,6-dimethyl-3,4,5,6-tetrahydroazocin-2(1*H*)-one (489)

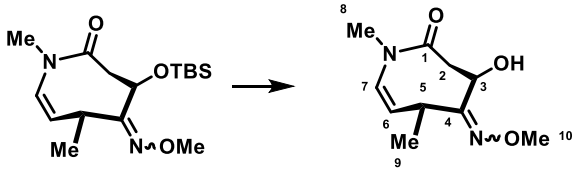


429 489

Ketone **429** (412 mg, 4.94 mmol) was added to a stirring solution of ketone (147 mg, 0.49 mmol) in pyridine (5.6 mL). The reaction was stirred for 16 h at room temperature before being concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and washed with 1 M aq. HCl (10 mL) and brine (10 mL). The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound (154 mg, 96%) as a colourless oil; ν_{max} / cm^{-1}: 2929 (m), 2956 (m), 1644 (s), 1462 (m), 1390 (m), 1040 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.79 (1H, dd, *J* = 8.5, 2.5 Hz, C**7**-<u>H</u>), 5.29 (1H, dd, *J* = 8.5, 4.0 Hz, C**6**-<u>H</u>), 4.57 (1H, dd, *J* = 10.5, 6.5 Hz, C**3**-<u>H</u>), 4.08 (1H, m, C**5**-<u>H</u>), 3.79 (3H, s, C**13**-<u>H_3</u>), 3.20 (1H, m, 1 × C**2**-<u>H_2</u>), 2.90 (3H, s, C**8**-<u>H_3</u>), 2.61 (1H, dd, *J* = 11.5, 6.5 Hz, 1 × C**2**-<u>H_2</u>), 1.34 (3H, d, *J* = 7.5 Hz, C**9**-<u>H_3</u>), 0.87 (9H, s, C**12**-<u>H_3</u>), 0.10 (3H, s, C**10**-<u>H_3</u>), 0.06 (3H, s, C**10**-<u>H_3</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1 (C**7**), 158.9 (C**4**), 128.9 (C**7**), 128.1 (C**6**), 72.6 (C**3**), 61.8 (C**13**), 42.5 (C**2**), 34.1

(C**8**), 29.7 (C**5**), 25.9 (C**12**), 19.2 (C**9**), 18.2 (C**11**), -4.6 (C**10**), -5.0 (C**10**); HRMS: (ESI$^+$) Calculated for $C_{16}H_{31}N_2O_3Si$: 327.2098. Found [M + Na$^+$]: 327.2113.

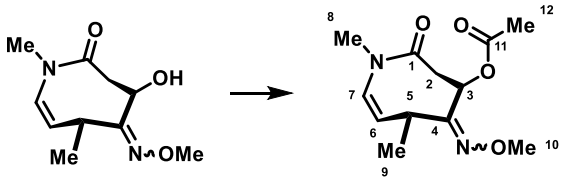
(5*Z*,7*Z*)-4-Hydroxy-5-(methoxyimino)-1,6-dimethyl-3,4,5,6-tetrahydroazocin-2(1*H*)-one (490)



489 **490**

TBAF (0.153 mL, 0.153 mmol, 1 M THF) was added to a stirring solution of silyl ether **489** (50 mg, 0.153 mmol) in THF (1.5 mL). The reaction was stirred at room temperature for 2 h before the addition of water (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (75% EtOAc/hexane) provided the title compound (29 mg, 89%) as a pale yellow oil; ν_{max} / cm^{-1}: 3363 (br.), 2936 (w), 1631 (s), 1455 (m), 1388 (m), 1041 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.94 (1H, dd, *J* = 7.5, 1.5 Hz, C**7**-H), 5.50 (1H, dd, *J* = 8.0, 7.5 Hz, C**6**-H), 4.46 (1H, dd, *J* = 10.5, 3.5 Hz, C**3**-H), 3.83 (3H, s, C**10**-H_3), 3.58 (1H, br. s, OH), 3.12 (1H, m, C**5**-H), 2.95 (3H, s, C**8**-H_3), 2.83 (1H, dd, *J* = 11.5, 3.5 Hz, 1 × C**2**-H_2), 2.73 (1H, m, 1 × C**2**-H_2), 1.39 (3H, d, *J* = 7.0 Hz, C**9**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2 (C**1**), 157.3 (C**4**), 129.8 (C**7**), 125.9 (C**6**), 69.0 (C**3**), 62.4 (C**10**), 44.3 (C**2**), 34.5 (C**8**), 33.6 (C**5**), 17.4 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{10}H_{16}N_2NaO_3$: 235.1053. Found [M + Na$^+$]: 235.1052.

(5*Z*,7*Z*)-5-(Methoxyimino)-1,6-dimethyl-2-oxo-1,2,3,4,5,6-hexahydroazocin-4-yl acetate (491)

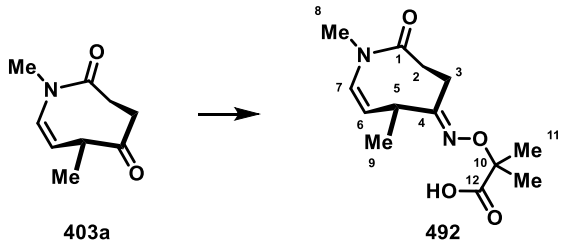


490 **491**

General Procedure N: Oxime **490** (29.2 mg, 0.137 mmol), $Pd(OAc)_2$ (5.1 mg, 0.023 mmol) and $PhI(OAc)_2$ (109 mg, 0.34 mmol) were employed in AcOH:Ac_2O (2.3 mL, 1:1). The reaction was heated at 100 °C for 3 h. FCC (60% EtOAc/hexane) provided the title compound (37 mg, 40%) as an orange oil; ν_{max} / cm^{-1}: 2939 (w), 1744 (s), 1646 (s), 1372 (m), 1224 (s), 1044 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.91 (1H, dd, *J* = 8.5, 2.0 Hz, C**7**-H), 5.55 (1H, dd, *J* = 10.0, 5.5, Hz, C**3**-H), 5.42 (1H, dd, *J* = 8.5, 6.0 Hz, C**6**-H), 3.97 (1H, m, C**5**-H), 3.83 (3H, s, C**10**-H_3), 3.19 (1H, dd, *J* = 12.0, 10.0 Hz, 1 × C**2**-H_2), 2.94 (3H, s, C**8**-H_3), 2.83 (1H, dd, *J* = 12.0, 5.5 Hz, 1 × C**2**-H_2), 2.05 (3H, s, C**12**-H_3), 1.31 (3H, d, *J* = 7.5 Hz, C**9**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.3 (C**11**), 168.2 (C**1**), 155.4 (C**4**), 130.1 (C**7**), 127.4

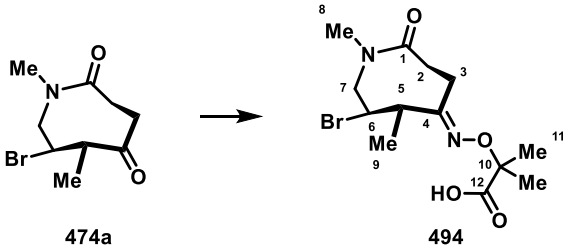
(C**6**), 71.7 (C**3**), 62.2 (C**10**), 39.2 (C**2**), 34.1 (C**8**), 30.3 (C**5**), 21.1 (C**12**), 17.2 (C**9**); HRMS: (ESI^+) Calculated for $C_{12}H_{18}N_2NaO_4$: 277.1159. Found [M + Na^+]: 277.1146.

2-((((5*E*,7*Z*)-1,6-Dimethyl-2-oxo-1,3,4,6-tetrahydroazocin-5(2*H*)-ylidene)amino)oxy)-2-methylpropanoic acid (492)



General Procedure M: Ketone **403a** (100 mg, 0.60 mmol), oxime hydrochloride (140 mg, 0.90 mmol) and NaOAc (147 mg, 1.80 mmol) were employed. The reaction was carried out at reflux for 1 h. The title compound (161 mg, 100%, 8:1 d.r.) was afforded as a pale yellow oil which solidified upon standing; **Data for the major diastereomer:** m.p. 107–109 °C (CH_2Cl_2);; ν_{max} / cm^{-1}: 3437 (br.), 2982 (w), 2935 (w), 1722 (m), 1605 (s), 1455 (m), 1386 (m), 1155 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.73 (1H, br., O<u>H</u>), 6.01 (1H, dd, *J* = 8.0, 1.5 Hz, C**7**-<u>H</u>), 5.21 (1H, dd, *J* = 8.0, 8.0 Hz, C**6**-<u>H</u>), 3.29 (1H, ddd, *J* = 15.5, 6.5, 4.0 Hz, 1 × C**3**-<u>H_2</u>), 3.08–3.00 (4H, m, C**5**-<u>H</u>, C**8**-<u>H_3</u>), 2.64–2.61 (2H, m, C**2**-<u>H_2</u>), 2.33 (1H, ddd, *J* = 15.5, 10.5, 5.5 Hz, 1 × C**3**-<u>H_2</u>), 1.50 (3H, s, C**11**-<u>H_3</u>), 1.49 (3H, s, C**11**-<u>H_3</u>), 1.20 (3H, d, *J* = 7.0 Hz, C**9**-<u>H_3</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.5 (C**12**), 173.3 (C**1**), 159.9 (C**4**), 130.0 (C**7**), 128.3 (C**6**), 81.6 (C**10**), 37.0 (C**5**), 34.2 (C**8**), 32.0 (C**2**), 24.2 (C**11**), 22.9 (C**3**), 17.4 (C**9**); HRMS: (ESI^+) Calculated for $C_{13}H_{21}N_2O_4$: 269.1496. Found [M + H^+]: 269.1492; **Data for the major diastereomer:** *Characteristic signals only*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.85 (1H, dd, *J* = 8.5, 2.0 Hz, C**7**-<u>H</u>), 5.33 (1H, dd, *J* = 8.5, 6.0 Hz, C**6**-<u>H</u>), 4.00 (1H, m, C**5**-<u>H</u>).

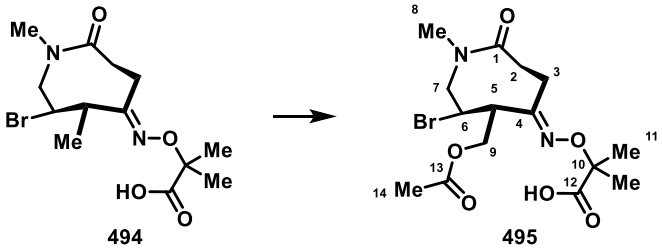
(*E*)-2-(((7-Bromo-1,6-dimethyl-2-oxoazocan-5-ylidene)amino)oxy)-2-methylpropanoic acid (494)



General Procedure M: Ketone **474a** (50.3 mg, 0.20 mmol), oxime hydrochloride (94.4 mg, 0.60 mmol) and NaOAc (115 mg, 1.40 mmol) were employed. The reaction was carried out at reflux for 1 h. The title compound (65 mg, 93%) was afforded as a colourless foam; ν_{max} / cm^{-1}: 3125 (br.), 2936 (w), 1722 (m), 1600 (s), 1465 (m), 1158 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.36 (1H, br. s, O<u>H</u>), 4.17 (1H, br. m, C**7**-<u>H_2</u>), 3.94 (1H, ddd, *J* = 10.5, 3.5, 3.5 Hz, C**6**-<u>H</u>), 3.66 (1H, br. m, C**7**-<u>H_2</u>), 3.45 (1H,

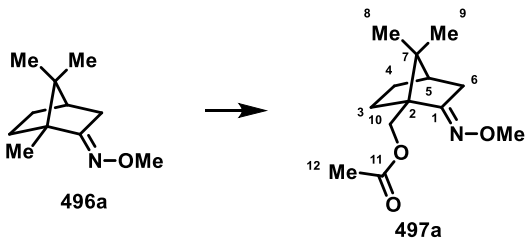
m, C**3**-H$_2$), 3.15 (3H, s, C**8**-H$_3$), 2.74–2.65 (2H, m, C**2**-H$_2$), 2.53 (1H, m, C**5**-H), 1.99 (1H, br. m, C**3**-H$_2$), 1.53 (3H, s, C**11**-H$_3$), 1.48 (3H, s, C**11**-H$_3$), 1.37 (3H, d, *J* = 7.0 Hz, C**9**-H$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.9 (C**1**), 174.5 (C**12**), 160.4 (C**4**), 81.6 (C**10**), 56.3 (C**7**), 53.6 (C**6**), 45.6 (C**5**), 37.8 (C**8**), 31.9 (C**2**), 27.5 (C**3**), 24.6, 23.5 (C**11**), 19.3 (C**9**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{21}BrN_2NaO_4$: 371.0577. Found [M + Na$^+$]: 371.0613.

(*E*)-2-(((6-(Acetoxymethyl)-7-bromo-1-methyl-2-oxoazocan-5-ylidene)amino)oxy)-2-methylpropanoic acid (495)



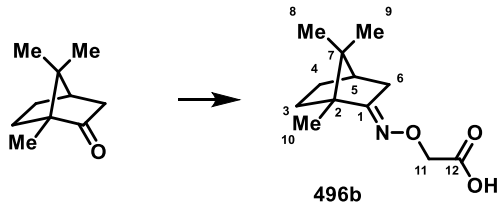
General Procedure N: Oxime **494** (100 mg, 0.286 mmol), Pd(OAc)$_2$ (6.4 mg, 0.029 mmol) and PhI(OAc)$_2$ (92 mg, 0.286 mmol) were employed in AcOH:Ac$_2$O (2.9 mL, 1:1). The reaction was heated at 80 °C for 16 h. The crude reaction mixture was dissolved in Et$_2$O (5 mL) and extracted with 10% aq. K_2CO_3 (3 × 5 mL). The aqueous layer was acidified to pH 1 with conc. HCl and extracted with Et$_2$O (3 × 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound (129 mg, 92%) as a yellow foam; ν_{max} / cm^{-1}: 3445 (br.), 2985 (w), 1732 (s), 1604 (s), 1466 (s), 1232 (s), 1164 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.02 (1H, br. s, OH), 4.56 (1H, dd, *J* = 10.5, 4.0 Hz, C**9**-H$_2$), 4.35 (1H, dd, *J* = 10.5, 10.0 Hz, C**9**-H$_2$), 4.24 (1H, br. m, C**7**-H$_2$), 4.00 (1H, ddd, *J* = 11.0, 3.5, 3.0 Hz, C**6**-H), 3.64 (1H, br. m, C**7**-H$_2$), 3.51 (1H, ddd, *J* = 13.0, 6.0, 5.5 Hz, C**3**-H$_2$), 3.16 (3H, br. s, C**8**-H$_3$), 2.81 (1H, br. m, C**5**-H), 2.75–2.63 (2H, br. m, C**2**-H$_2$), 2.00 (3H, s, C**14**-H$_3$), 1.97 (1H, br. m, C**3**-H$_2$), 1.51 (3H, s, C**11**-H$_3$), 1.48 (3H, s, C**11**-H$_3$); *The ^{13}C signal for C1 was not visible because the signal was broad.* ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.7 (C**12**), 171.0 (C**13**), 158.2 (C**4**), 81.8 (C**10**), 66.8 (C**9**), 51.4 (C**6**), 49.0 (C**5**), 37.8 (C**8**), 32.1 (C**2**), 27.9 (C**3**), 24.4 (C**11**), 23.5 (C**11**), 20.8 (C**14**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{22}N_2O_6Br$: 405.0661. Found [M + H$^+$]: 405.0665.

((1*R*,4*R*,*E*)-2-(Methoxyimino)-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methyl acetate (497a)



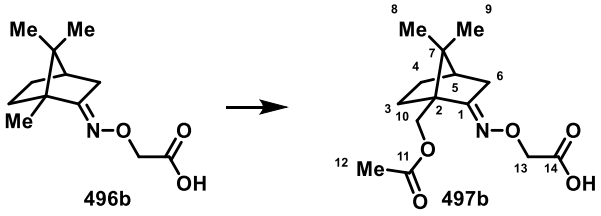
General Procedure N: *Oxime **496a** was prepared according to a literature procedure*[301]: Oxime **496a** (90.7 mg, 0.500 mmol), $Pd(OAc)_2$ (5.60 mg, 0.0250 mmol) and $PhI(OAc)_2$ (322 mg, 1.00 mmol) were employed in AcOH:Ac_2O (5 mL, 1:1). The reaction was heated at 80 °C for 3 h and a separate identical reaction was heated at 90 °C for 9 h. The crude reaction mixtures were concentrated *in vacuo* and a yield of product **497a** (<10% yield obtained at 80 °C for 3 h; 60% yield obtained at 90 °C for 9 h) was measured by analysis of the ^{1}H NMR of the crude material against an internal standard (1,4-DNB). *A pure sample of product **497a** was obtained by Ambler, the spectroscopic properties of which were consistent with that available in the literature.*[301]

2-((((1*S*,4*R*,*E*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)amino)oxy)acetic acid (496b)



General Procedure M: Camphor (305 mg, 2.00 mmol), oxime hydrochloride (328 mg, 3.00 mmol) and NaOAc (493 mg, 6.00 mmol) were employed. The reaction was carried out at reflux for 1 h. The title compound (207 mg, 92%) was afforded as a colourless foam; ν_{max} / cm^{-1}: 3036 (br. s), 2957 (s), 1731 (s), 1239 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.62–4.53 (2H, m, C**11**-$\underline{H}_2$), 2.58 (1H, dd, J = 18.0, 4.0 Hz, C**6**-$\underline{H}_2$), 2.07 (1H, d, J = 18.0 Hz, C**6**-$\underline{H}_2$), 1.91 (1H, m, C**5**-$\underline{H}$), 1.84 (1H, m, C**5**-$\underline{H}_2$), 1.72 (1H, ddd, J = 12.5, 12.0, 4.0 Hz, C**4**-$\underline{H}_2$), 1.45 (1H, m, C**4**-$\underline{H}_2$), 1.24 (1H, m, C**3**-$\underline{H}_2$), 0.99 (3H, s, C**10**-$\underline{H}_3$), 0.92 (3H, s, C**8**/**9**-$\underline{H}_3$), 0.80 (3H, s, C**8**/**9**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.1 (C**12**), 173.4 (C**1**), 70.0 (C**11**), 52.4 (C**7**), 48.5 (C**2**), 43.8 (C**5**), 34.1 (C**6**), 32.7 (C**3**), 27.3 (C**4**), 19.5, 18.6 (C**8**, C**9**), 11.1 (C**10**); HRMS: (ESI$^-$) Calculated for $C_{12}H_{18}NO_3$: 224.1287. Found [M - H]$^-$: 224.1293.

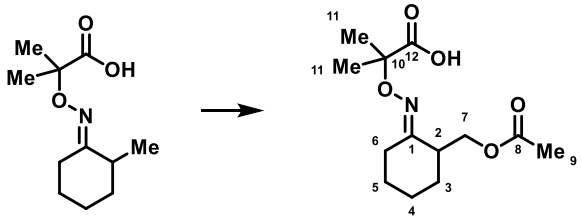
2-((((1*R*,4*R*,*E*)-1-(Acetoxymethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ylidene)amino)oxy)acetic acid (497b)



General Procedure N: Oxime **496b** (113 mg, 0.500 mmol), $Pd(OAc)_2$ (5.60 mg, 0.0250 mmol) and $PhI(OAc)_2$ (322 mg, 1.00 mmol) were employed in AcOH:Ac_2O (5 mL, 1:1). The reaction was heated at 80 °C for 3 h and a separate identical reaction was heated at 90 °C for 9 h. The crude reaction mixtures were concentrated *in vacuo* and a yield of product **497b** (75% yield obtained at 80 °C for 3 h; 75% yield obtained at 90 °C for 9 h) was measured by analysis of the ^{1}H NMR of the crude material against an internal standard (1,4-DNB). A purer sample of product **497b** was obtained by dissolving the crude

reaction mixture in Et_2O (5 mL) and extracting with 10% aq. K_2CO_3 (3 × 5 mL). The aqueous layer was acidified to pH 1 with conc. HCl and extracted with Et_2O (3 × 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound in a suitable purity for analysis; ν_{max} / cm^{-1}: 3125 (br.), 2923 (m), 1739 (s), 1243 (s), 1073 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.60 (1H, d, *J* = 17.0 Hz, C**13**-$\underline{H}_2$), 4.54 (1H, d, *J* = 17.0 Hz, C**13**-$\underline{H}_2$), 4.31 (1H, d, *J* = 12.0 Hz, C**10**-$\underline{H}_2$), 4.22 (1H, d, *J* = 12.0 Hz, C**10**-$\underline{H}_2$), 2.62 (1H, m, C**6**-$\underline{H}_2$), 2.08–2.00 (4H, s, 1 × C**6**-$\underline{H}_2$, 3 × C**12**-$\underline{H}_3$), 2.00–1.83 (3H, m, 1 × C**3**-$\underline{H}_2$, 1 × C**4**-$\underline{H}_2$, 1 × C**5**-$\underline{H}$), 1.48 (1H, m, C**3**-$\underline{H}_2$), 1.28 (1H, m, C**4**-$\underline{H}_2$), 1.01 (3H, s, C**8**/**9**-$\underline{H}_3$), 0.91 (3H, s, C**8**/**9**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.3 (C**14**), 171.4 (C**11**), 169.2 (C**1**), 70.0 (C**13**), 61.7 (C**10**), 54.6 (C**7**), 48.7 (C**2**), 44.7 (C**5**), 33.8 (C**6**), 28.3 (C**3**), 26.9 (C**4**), 20.1, 19.7 (C**8**/**9**); HRMS: (ESI^+) Calculated for $C_{14}H_{22}NO_5$: 284.1492. Found $[M + H]^+$: 284.1491.

(*E*)-2-(((2-(Acetoxymethyl)cyclohexylidene)amino)oxy)-2-methylpropanoic acid (507)

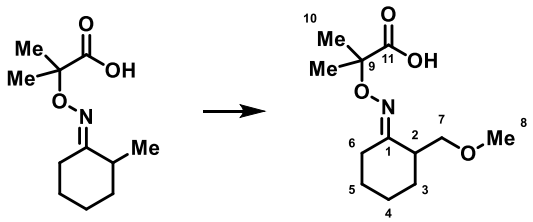


506 507

General Procedure N: *Oxime **506** was prepared by Ambler according to a literature procedure*[305]: Oxime[305] (53.3 mg, 0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol) and $PhI(OAc)_2$ (121 mg, 0.375 mmol) were employed in AcOH:Ac_2O (2.5 mL, 1:1). The reaction was heated at 60 °C for 16 h. The crude reaction mixture was concentrated *in vacuo* and analysed by ^1H NMR against 1,4-DNB as an internal standard which revealed that the desired product (76%, 5:1 d.r.) had been formed. A purified sample of the title compound was obtained by dissolving the crude reaction mixture in Et_2O (5 mL) and extracting with 10% aq. K_2CO_3 (3 × 5 mL). The aqueous layer was acidified to pH 1 with conc. HCl and extracted with Et_2O (3 × 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound for characterisation purposes; **Data for the major diastereomer:** ν_{max} / cm^{-1}: 2933 (m), 2860 (w), 1735 (s), 1303 (m), 1169 (m), 1087 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.84 (1H, br. s, O$\underline{H}$), 4.31 (1H, dd, *J* = 11.0, 7.0 Hz, 1 × C**7**-$\underline{H}_2$), 4.10 (1H, dd, *J* = 11.0, 6.0 Hz, 1 × C**7**-$\underline{H}_2$), 3.00 (1H, m, 1 × C**6**-$\underline{H}_2$), 2.56 (1H, m, C**2**-$\underline{H}$), 2.07–1.92 (5H, m, 1 × C**3**-$\underline{H}_2$, 1 × C**6**-$\underline{H}_2$, 3 × C**9**-$\underline{H}_3$), 1.82–1.74 (2H, m, 1 × C**4**-$\underline{H}_2$, 1 × C**5**-$\underline{H}_2$), 1.60–1.37 (9H, m, 1 × C**3**-$\underline{H}_2$, 1 × C**4**-$\underline{H}_2$, 1 × C**5**-$\underline{H}_2$, 6 × C**11**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.3 (C**12**), 171.2 (C**8**), 162.0 (C**1**), 81.1 (C**10**), 64.3 (C**7**), 41.7 (C**2**), 30.3 (C**3**), 26.0 (C**5**), 24.9 (C**6**), 24.2 (C**4**), 24.2 (C**11**), 21.0 (C**9**); HRMS: (ESI^+) Calculated for $C_{13}H_{21}NNaO_5$: 294.1312. Found $[M + Na]^+$: 294.1318; **Data for the minor diastereomer:** *Characteristic signals only*: ^1H NMR ($CDCl_3$, 400 MHz): δ 3.17 (1H, m, C**2**-$\underline{H}$).

Method for the methanolysis of crude reaction mixtures: *When the reaction was run in solvents other than AcOH:Ac$_2$O, a methanolic work-up was required to break up PhI(OAc)$_2$ based side products.* The crude reaction mixture was dissolved in MeOH (5 mL), to which K_2CO_3 (100 mg) was added. The mixture was stirred for 15 minutes before being concentrated *in vacuo*. The resulting residue was dissolved in water (10 mL) and extracted with Et_2O (5 mL). The aqueous phase was acidified (pH ~1) with conc. HCl and extracted with Et_2O (3 × 5 mL). The resulting organic extracts were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide β-oxygenation products.

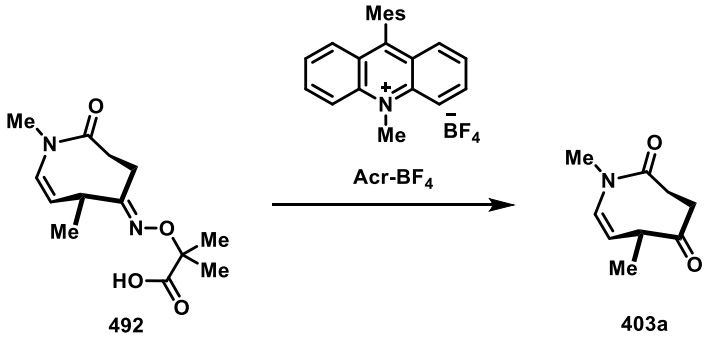
(*E*)-2-(((2-(Methoxymethyl)cyclohexylidene)amino)oxy)-2-methylpropanoic acid (508a)



506 **508a**

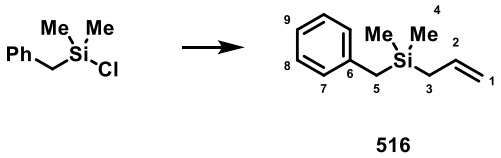
General Procedure N: Oxime **506** (32.0 mg, 0.15 mmol), $Pd(OAc)_2$ (3.40 mg, 0.015 mmol) and $PhI(OAc)_2$ (72.5 mg, 0.225 mmol) were employed in MeOH (1.5 mL, 1:1). The reaction was heated at 80 °C for 16 h. The crude reaction mixture was concentrated *in vacuo* and analysed by ^{1}H NMR against 1,4-DNB as an internal standard which revealed that the desired product (75%, 5:2 d.r., A:B) had been formed. A purified sample of the title compound was obtained by dissolving the crude reaction mixture in Et_2O (5 mL) and extracting with 10% aq. K_2CO_3 (3 × 5 mL). The aqueous layer was acidified to pH 1 with conc. HCl and extracted with Et_2O (3 × 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound for characterisation purposes; ν_{max} / cm^{-1}: 2930 (m), 1714 (s), 1449 (w), 1171 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83 (1H, m, C**2**-H, B), 3.64–3.59 (2H, m, 1 × C**7**-H$_2$, A+B), 3.49 (1H, dd, *J* = 9.0, 5.5 Hz, C**7**-H$_2$, B), 3.37 (1H, dd, *J* = 9.5, 6.5 Hz, C**7**-H$_2$, A), 3.34 (3H, s, C**8**-H$_3$, B), 3.32 (3H, s, C**8**-H$_3$, A), 2.99 (1H, m, C**6**-H$_2$, A), 2.50 (1H, m, C**2**-H, A), 2.34 (1H, m, C**6**-H$_2$, B), 2.17 (1H, m, C**6**-H$_2$, B), 2.02–1.95 (2H, m, 1 × C**3**-H$_2$, 1 × C**6**-H$_2$, A), 1.89 (1H, m, C**5**-H$_2$, B), 1.83–1.71 (4H, m, 1 × C**3**-H$_2$ (B), 2 × C**4**-H$_2$ (A), 1 × C**5**-H$_2$ (B), 1.64–1.53 (5H, m, 1 × C**3**-H$_2$ (B), 1 × C**4**-H$_2$ (B), 3 × C**10**-H$_3$ (B)), 1.53–1.33 (11H, m, 1 × C**3**-H$_2$ (A), 1 × C**4**-H$_2$ (B), 6 × C**10**-H$_3$ (A), 3 × C**10**-H$_3$ (B)); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.9 (C**11**, A), 176.6 (C**11**, B), 81.4 (C**9**, B), 81.2 (C**9**, A), 73.6 (C**7**, B), 72.7 (C**7**, A), 59.0 (C**8**, B), 58.9 (C**8**, A), 42.7 (C**2**, A), 33.5 (C**2**, B), 30.5 (C**3**, A), 28.8 (C**6**, B), 27.0 (C**3**, B), 26.3 (C**5**, B), 26.1 (C**5**, A), 25.4 (C**10**, B), 25.1 (C**6**, A), 24.4, 24.4 (C**4** (A), C**10** (A), C**10** (A)), 22.9 (C**10**, B), 21.6 (C**4**, B); HRMS: (ESI$^+$) Calculated for $C_{12}H_{22}NO_4$: 244.1543. Found $[M + H]^+$: 244.1540.

Preliminary procedure for the removal of carboxylic acid oximes under photoredox catalysed conditions



The procedure for the removal of carboxylic acid oximes under photoedox catalysed conditions was adapted from a literature procedure[288]: A flame-dried, 1.7 mL vial, equipped with a stir bar, was charged with IMes-Acr catalyst **Acr-BF_4** (2.0 mg, 0.005 mmol), sealed with a rubber septum and cooled to 0 °C before being purged with argon for 5 minutes. Carboxylic acid oxime **492** (27.0 mg, 0.100 mmol) in anhydrous 1,2-DCE (0.5 mL), 2,6-lutidine (0.030 mL, 0.025 mmol) and thiophenol (0.020 mL, 0.020 mmol) were added by syringe. The stirring reaction was irradiated with two 15 W, royal blue, PAR38 LED floodlamps (Caution: the lamps were only turned on when suitably shaded so as to avoid shining the light into eyes) for 24 h at room temperature. The reaction mixture was concentrated *in vacuo* and analysed by ^{1}H NMR where the product **403a** was measured by integration to be in an approximately 1:1 molar ratio with starting material **492**.

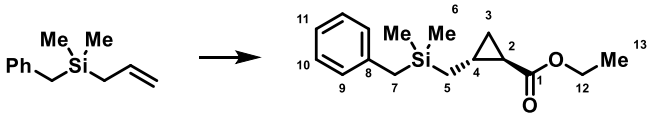
Allyl(benzyl)dimethylsilane (516)



Magnesium ribbon (2.92 g, 120 mmol) was added to a flame-dried three-necked flask fitted with a 250 mL dropping funnel, rubber septum and attached to a Schlenk line. The flask was evacuated and refilled with nitrogen three times before the addition of dry Et_2O (44 mL) and a crystal of iodine. The suspension was stirred until colourless and then benzylchloride (2.90 mL, 120 mmol) in Et_2O (100 mL) was added dropwise at such a rate as to maintain reflux. Meanwhile, allylchlorodimethylsilane (11.2 mL, 74.0 mmol) and Et_2O (200 mL) were added to a separate flask under argon, which was cooled to 0 °C. The benzylmagnesium chloride solution was transferred to the silane solution by canula over 5 minutes. The reaction mixture was warmed to room temperature then heated at reflux for 5 h. The reaction was cooled to room temperature then quenched by the addition of sat. aq. NH_4Cl (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (Hexane) provided the title compound (10.6 g, 75%)

as a colourless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (2H, dd, *J* = 7.5, 7.5 Hz, C**8**-H), 7.08 (1H, t, *J* = 7.5 Hz, C**9**-H), 7.00 (2H, d, *J* = 7.5 Hz, C**7**-H), 5.77 (1H, m, C**2**-H), 4.87 (1H, m, 1 × C**1**-H_2), 4.84 (1H, m, 1 × C**1**-H_2), 2.11 (2H, s, C**5**-H_2), 1.53 (2H, m, C**3**-H_2), 0.02 (6H, s, C**4**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.1 (C**6**), 134.8 (C**2**), 128.3, 128.3 (C**7**, C**8**), 124.1 (C**9**), 113.4 (C**1**), 25.2 (C**5**), 22.9 C**3**), -3.9 (C**4**). *The spectroscopic properties of this compound were consistent with the data available in the literature*[364]

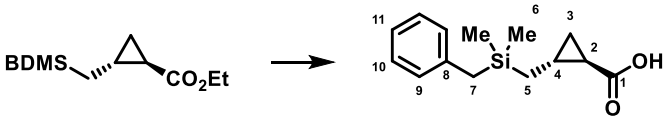
Ethyl (1*R,2*R**)-2-((benzyldimethylsilyl)methyl)cyclopropane-1-carboxylate (519)**



516 519

Allylsilane **516** (10.6 g, 55.8 mmol) in CH_2Cl_2 (56 mL, 1.0 M) was added to a flask containing $Rh_2(OAc)_4$ (246 mg, 0.558 mmol) under argon. Ethyl diazoacetate (8.80 mL, 83.7 mmol) in CH_2Cl_2 (8.80 mL) was added dropwise over 14 h. The resulting solution was concentrated *in vacuo*. FCC (4–6% EtOAc/hexane) provided the title compound (8.87 g, 57%, 5:2 d.r., A:B) as a pale orange oil; ν_{max} / cm^{-1}: 2956 (w), 1722 (s), 1493 (m), 1248 9m), 1193 (m), 1162 (s), 837 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): *Some signals for the minor diastereomer B could not be assigned*: δ 7.23–7.20 (4H, m, C**10**-H, A+B), 7.10–7.05 (2H, m, C**11**-H, A+B), 7.02–6.98 (4H, m, C**9**-H, A+B), 4.17–4.09 (4H, m, C**12**-H_2, A+B), 2.13–2.12 (4H, m, C**7**-H_2, A+B), 1.30–1.19 (9H, m, 1 × C**2**-H (A), 1 × C**3**-H_2 (A), 1 × C**4**-H (A), 6 × C**13**-H_3 (A+B), 1.04 (1H, m, C**3**-H_2, B), 0.87–0.82 (3H, m, 1 × C**3**-H_2 (B), 2 × C**5**-H_2 (B)), 0.77 (1H, dd, *J* = 14.5, 5.0 Hz, C**5**-H_2, A), 0.63 (1H, m, C**3**-H_2, A), 0.44 (1H, dd, *J* = 14.5, 7.5 Hz, C**5**-H_2, A); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.6 (C**1**, A), 173.1 (C**1**, B), 140.2 (C**8**, B), 140.0 (C**8**, A), 128.3, (C**10**, A), 128.3 (C**10**, B), 128.2 (C**9**, B), 128.2 (C**9**, A), 124.2 (C**11**, A), 124.1 (C**11**, B), 60.4 (C**12**, A), 60.3 (C**12**, B), 25.6, 25.6 (C**7**, A+B), 22.3 (C**4**, A), 19.2 (C**5**, A), 19.1 (C**4**, B), 18.9 (C**2**, A), 17.7 (C**2**, B), 17.4 (C**3**, A), 15.0 (C**3**, B), 14.5 (C**13**, B), 14.5 (C**13**, A), 12.4 (C**5**, B), -3.3 (C**6**, A), -3.4 (C**6**, A), -3.4 (C**6**, B), -3.5 (C**6**, B); HRMS: (ESI^+) Calculated for $C_{16}H_{24}NaO_2Si$: 299.1438. Found $[M + Na]^+$: 299.1441.

(1*R,2*R**)-2-((Benzyldimethylsilyl)methyl)cyclopropane-1-carboxylic acid (520)**

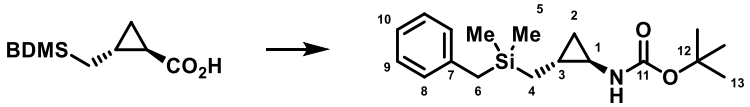


519 520

Ethyl ester **519** (6.39 g, 23.1 mmol) was dissolved in MeOH (56 mL) and 4 M aq. NaOH (29 mL, 116 mmol). The reaction was heated at reflux for 2 h at which point it was complete by TLC. MeOH was removed *in vacuo* and the aqueous phase was washed with Et_2O (30 mL). The aqueous phase was

acidified with conc. HCl and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the title compound (971 mg, 99%, 5:2 d.r., A:B) as a pale yellow oil; ν_{max} / cm^{-1}: 3300 (br.), 2959 (w), 1688 (s), 1450 (m), 1231 (m), 837 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.23–7.19 (4H, m, C**10**-H, A+B), 7.09–7.05 (2H, m, C**11**-H, A+B), 7.01–6.98 (4H, m, C**9**-H, A+B), 2.14–2.12 (4H, s, C**7**-H_2, A+B), 1.68 (1H, m, 1 × C**4**-H, B), 1.41–1.25 (4H, m, 2 × C**2**-H (A+B), 1 × C**3**-H_2 (A), 1 × C**4**-H (A)), 1.12 (1H, m, 1 × C**3**-H_2, B), 0.91–0.77 (4H, m, 1 × C**3**-H_2 (B), 1 × C**5**-H_2 (A), 2 × C**5**-H_2 (B)), 0.72 (1H, m, C**3**-H_2, A), 0.43 (1H, dd, *J* = 14.5, 8.5 Hz, C**5**-H_2, A), 0.05 (3H, s, C**6**-H_3, A), 0.04 (3H, s, C**6**-H_3, A), 0.02 (3H, s, C**6**-H_3, B), 0.02 (3H, s, C**6**-H_3, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 181.1 (C**1**, A), 179.8 (C**1**, B), 140.1 (C**8**, B), 139.9 (C**8**, A), 128.4, (C**10**, A), 128.3 (C**10**, B), 128.2 (C**9**, B), 128.2 (C**9**, A), 124.2 (C**11**, A), 124.1 (C**11**, B), 25.7 (C**7**, B), 25.6 (C**7**, A), 22.1 (C**2**, A), 20.2 (C**4**, A), 19.3 (C**5**, A), 19.2, 19.1 (C**2**, C**4**, B), 18.4 (C**3**, A), 16.0 (C**3**, B), 12.4 (C**5**, B), -3.31- -3.37 (4 × C6, A+B); HRMS: (ESI^+) Calculated for $C_{14}H_{20}NaO_2Si$: 271.1125. Found $[M + Na]^+$: 271.1138.

***tert*-Butyl ((1*R*,2R**)-2-((benzyldimethylsilyl)methyl)cyclopropyl)carbamate (521)**

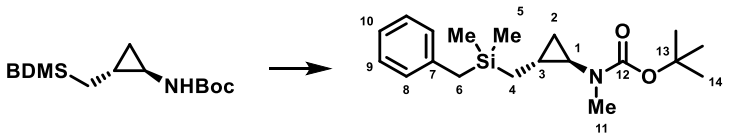


520 **521**

General Procedure D: Carboxylic acid **520** (7.44 g, 30.0 mmol, 5:2 d.r.) was employed and the reaction was heated for 72 h. FCC (10% EtOAc/hexane) provided the major diastereomer (4.98 g, 67%) of title compound as a colourless oil and the minor diastereomer (2.15 g, 29%) as a colourless oil; *Note: The two diastereomers could be separated at this point by FCC (10% Et_2O/hexane) but were typically carried on as a mixture to aid material throughput;* **Data for the *trans*-diastereomer *trans*-521:** ν_{max} / cm^{-1}: 3333 (br.), 2975 (w), 1703 (s), 1493 (m), 1366 (m), 1248 (s), 1169 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20 (2H, m, C**9**-H), 7.06 (1H, m, C**10**-H), 6.99 (2H, d, *J* = 7.5 Hz, C**8**-H), 4.60 (1H, br. s, NH), 2.17 (1H, br. m, C**1**-H), 2.12 (2H, s, C**6**-H_2), 1.44 (9H, s, C**13**-H_3), 0.81 (1H, dd, *J* = 14.5, 5.5 Hz, C**4**-H_2), 0.71 (1H, br. m, C**3**-H), 0.64 (1H, m, C**2**-H_2), 0.42 (1H, m, C**2**-H_2), 0.30 (1H, br. m, C**4**-H_2), 0.02 (3H, s, C**5**-H_3), 0.01 (3H, s, C**5**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.6 (C**11**), 140.3 (C**7**), 128.3 (C**9**), 128.2 (C**8**), 124.1 (C**10**), 79.4 (C**12**), 31.0 (C**1**), 28.5 (C**13**), 25.8 (C**6**), 18.3 (C**4**), 16.1 (C**2**), 15.9 (C**3**), -3.2 (C**5**), -3.3 (C**5**); HRMS: (ESI^+) Calculated for $C_{18}H_{29}NNaO_2Si$: 342.1860. Found $[M + Na]^+$: 342.1853; **Data for the *cis*-diastereomer *cis*-521:** ν_{max} / cm^{-1}: 3318 (br.), 2975 (w), 1700 (s), 1493 (s), 1365 (m), 1248 (m), 1169 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20 (2H, m, C**9**-H), 7.06 (1H, t, *J* = 7.5 Hz, C**10**-H), 7.00 (2H, m, C**8**-H), 4.53 (1H, br. s, NH), 2.53 (1H, m, C**1**-H), 2.13 (2H, s, C**6**-H_2), 1.46 (9H, s, C**13**-H_3), 0.91–0.77 (3H, m, 1 × C**2**-H_2, 1 × C**3**-H, 1 × C**4**-H_2), 0.24 (1H, dd, *J* = 15.0, 11.0 Hz, C**4**-H_2), 0.03 (3H, s, C**5**-H_3), 0.02 (3H, s, C**5**-H_3), -0.01 (1H, m, 1 × C**2**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.0 (C**11**), 140.2 (C**7**), 128.3 (C**9**), 128.2 (C**8**), 124.1 (C**10**), 79.4 (C**12**),

28.5 (C**13**), 27.3 (C**1**), 25.8 (C**6**), 13.9 (C**2**), 12.7 (C**3**), 12.5 (C**4**), -3.2 (C**5**), -3.3 (C**5**); HRMS: (ESI^+) Calculated for $C_{18}H_{29}NNaO_2Si$: 342.1860. Found $[M + Na]^+$: 342.1869.

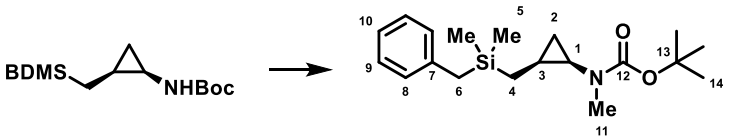
***tert*-Butyl ((1*R*,2R**)-2-((benzyldimethylsilyl)methyl)cyclopropyl)(methyl)carbamate (*trans*-522)**



***trans*-521** ***trans*-522**

General Procedure G: Carbamate ***trans*-521** (4.98 g, 15.6 mmol) was employed in THF using NaH (300 mol%) and MeI (500 mol%). The reaction was run for 3 h at 50 °C. FCC (6% EtOAc/hexane) provided the title compound (4.43 g, 85%) as a colourless oil. *Note: This reaction was typically carried out as a mixture of diastereomers to aid material throughput*; ν_{max} / cm^{-1}: 2973 (w), 1697 (s), 1364 (s), 1152 (s), 837 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20 (2H, m, C**9**-H), 7.06 (1H, m, C**10**-H), 6.99 (2H, m, C**8**-H), 2.76 (3H, s, C**11**-H_3), 2.14–2.08 (3H, m, C**1**-H, 2 × C**6**-H_2), 1.44 (9H, s, C**14**-H_3), 1.06 (1H, dd, *J* = 14.5, 4.0 Hz, C**4**-H_2), 0.85 (1H, m, C**3**-H), 0.75 (1H, m, C**2**-H_2), 0.42 (1H, m, C**2**-H_2), 0.11 (1H, dd, *J* = 14.5, 11.5 Hz, C**4**-H_2), 0.03 (3H, s, C**5**-H_3), 0.02 (3H, s, C**5**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.1 (C**12**), 140.2 (C**7**), 128.3 (C**9**), 128.2 (C**8**), 124.1 (C**10**), 79.3 (C**13**), 38.6 (C**1**), 34.5 (C**11**), 28.7 (C**14**), 25.6 (C**6**), 18.5 (C**4**), 17.6 (C**1**), 16.4 (C**2**), -3.8 (C**5**), -3.2 (C**5**); HRMS: (ESI^+) Calculated for $C_{19}H_{31}NNaO_2Si$: 356.2016. Found $[M + Na]^+$: 356.2022.

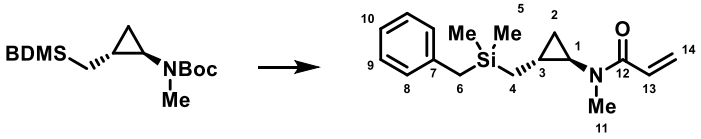
***tert*-Butyl ((1*R*,2S**)-2-((benzyldimethylsilyl)methyl)cyclopropyl)(methyl)carbamate (*cis*-522)**



***cis*-521** ***cis*-522**

General Procedure G: Carbamate ***cis*-521** (2.14 g, 6.70 mmol) was employed in THF using NaH (1.40 g, 33.5 mmol) and MeI (4.17 mL, 67.0 mmol). The reaction was run for 72 h at 50 °C. FCC (10% EtOAc/hexane) provided the title compound (1.71 g, 77%) as a pale yellow oil; ν_{max} / cm^{-1}: 2973 (w), 1697 (s), 1363 (s), 1248 (m), 1152 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20 (2H, m, C**9**-H), 7.06 (1H, m, C**10**-H), 6.99 (2H, m, C**8**-H), 2.82 (3H, s, C**11**-H_3), 2.52 (1H, m, C**1**-H), 2.13 (2H, m, C**6**-H_2), 1.45 (9H, s, C**14**-H_3), 1.00–0.84 (3H, m, 1 × C**2**-H_2, 1 × C**3**-H, 1 × C**4**-H_2), 0.15 (1H, m, C**2**-H_2), 0.07–0.01 (7H, m, 1 × C**4**-H_2, 6 × C**6**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.7 (C**12**), 140.3 (C**7**), 128.3 (C**9**), 128.2 (C**8**), 124.1 (C**10**), 79.3 (C**13**), 35.7 (C**11**), 35.3 (C**1**), 28.5 (C**14**), 25.6 (C**6**), 15.2 (C**3**), 13.3 (C**2**), 13.0 (C**4**), -3.1 (C**6**), -3.3 (C**6**); HRMS: (ESI^+) Calculated for $C_{19}H_{31}NNaO_2Si$: 356.2016. Found $[M + Na]^+$: 356.2027.

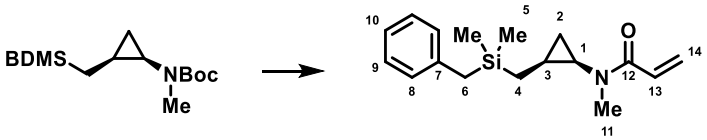
***N*-((1*R**,2*R**)-2-((Benzyldimethylsilyl)methyl)cyclopropyl)-*N*-methylacrylamide (*trans*-517)**



***trans*-522** ***trans*-517**

General Procedure H: Carbamate ***trans*-522** (2.62 g, 7.85 mmol) was employed. FCC (40% EtOAc/hexane) provided the title compound (2.06 g, 92%) as a golden oil; ν_{max} / cm^{-1}: 2954 (w), 1656 (s), 1616 (m), 1400 (m), 1248 (m), 839 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (2H, m, C**9**-H), 7.08 (1H, t, *J* = 7.5 Hz, C**10**-H), 6.99 (2H, m, C**8**-H), 6.80 (1H, dd, *J* = 17.0, 10.5 Hz, C**13**-H), 6.33 (1H, dd, *J* = 17.0, 2.0 Hz, C**14**-Ha), 5.65 (1H, dd, *J* = 10.5, 2.0 Hz, C**14**-Hb), 2.93 (3H, s, C**11**-H_3), 2.36 (1H, m, C**1**-H), 2.13 (2H, s, C**6**-H_2), 1.08 (1H, dd, *J* = 14.5, 4.0 Hz, C**4**-H_2), 0.99–0.87 (2H, m, 1 × C**3**-H, 1 × C**2**-H_2), 0.59 (1H, m, C**2**-H_2), 0.14 (1H, dd, *J* = 14.5, 10.0 Hz, C**2**-H_2), 0.05 (3H, s, C**6**-H_3),0.03 (3H, s, C**6**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2 (C**12**), 139.9 (C**7**), 129.1 (C**13**), 128.4 (C**9**), 128.2 (C**8**), 127.2 (C**14**), 124.3 (C**10**), 39.1 (C**1**), 34.1 (C**11**), 25.8 (C**6**), 18.7 (C**3**), 18.1 (C**4**), 17.5 (C**2**), -3.1 (C**5**), -3.2 (C**5**); HRMS: (ESI^+) Calculated for $C_{17}H_{26}NOSi$: 288.1778. Found $[M + H]^+$: 288.1786.

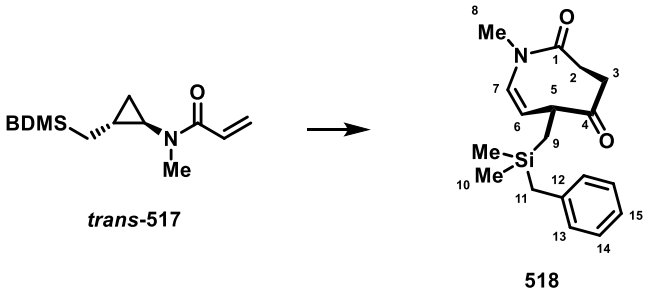
***N*-((1*R**,2*S**)-2-((Benzyldimethylsilyl)methyl)cyclopropyl)-*N*-methylacrylamide (*cis*-517)**



***cis*-522** ***cis*-517**

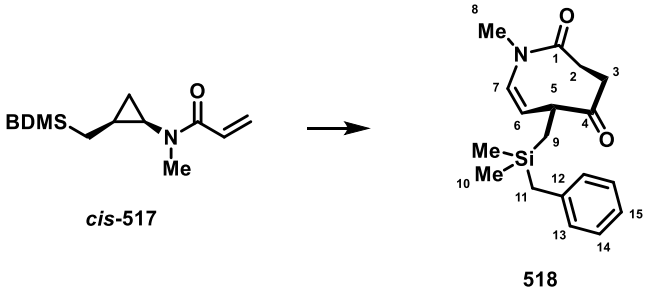
General Procedure H: Carbamate ***cis*-522** (1.71 g, 5.11 mmol) was employed. FCC (55% EtOAc/hexane) provided the title compound (1.27 g, 86%) as a pale yellow oil; ν_{max} / cm^{-1}: 2958 (w), 1655 (s), 1614 (m), 1399 (m), 1248 (m), 839 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (2H, m, C**9**-H), 7.06 (1H, m, C**10**-H), 6.97 (2H, m, C**8**-H), 6.80 (1H, dd, *J* = 17.0, 10.5 Hz, C**13**-H), 6.39 (1H, dd, *J* = 17.0, 2.0 Hz, C**14**-H_2), 5.65 (1H, dd, *J* = 10.5, 2.0 Hz, C**14**-H_2), 2.97 (3H, s, C**11**-H_3), 2.77 (1H, m, C**1**-H), 2.11 (2H, m, C**6**-H_2), 1.10–0.95 (2H, m, 1 × C**2**-H_2, 1 × C**3**-H), 0.89 (1H, d, *J* = 14.5 Hz, C**4**-H_2), 0.31 (1H, m, C**2**-H_2), 0.03 (3H, s, C**5**-H_3), 0.01 (3H, s, C**5**-H_3), -0.05 (1H, dd, *J* = 14.5, 12.0 Hz, C**4**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.8 (C**12**), 139.9 (C**7**), 128.8 (C**13**), 128.3 (C**9**), 128.2 (C**8**), 127.6 (C**14**), 124.2 (C**10**), 35.5 (C**1**), 35.1 (C**11**), 25.7 (C**6**), 16.6 (C**3**), 14.4 (C**2**), 13.6 (C**4**), -3.1 (C**5**), -3.3 (C**5**); HRMS: (ESI^+) Calculated for $C_{17}H_{25}NNaOSi$: 310.1598. Found $[M + Na]^+$: 310.1606.

(*Z*)-6-((Benzyldimethylsilyl)methyl)-1-methyl-1,3,4,6-tetrahydroazocine-2,5-dione (518)



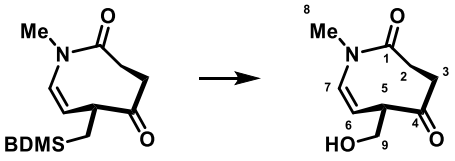
General Procedure I for the (7+1) carbonylative cycloaddition of *trans*-517: (*Screening conditions for optimum yield*) Acrylamide (28.7 mg, 0.10 mmol), $[Rh(cod)_2]OTf$ (3.5 mg, 0.0075 mmol), $As(PPh_3)_3$ (4.6 mg, 0.015 mmol) and fumaric acid (5.8 mg, 0.050 mmol) were employed, and the reaction was heated at 140 °C for 48 h. ^1H NMR analysis of the crude reaction mixture against 1,4-DNB as an internal standard indicated formation of the title compound (35%).

General Procedure I for the (7+1) carbonylative cycloaddition of *trans*-517: (*Multi-mmol scale reaction for material throughput*) Acrylamide (1.14 g, 3.96 mmol), $[Rh(cod)_2]OTf$ (139 mg, 0.30 mmol), $As(PPh_3)_3$ (182 mg, 0.59 mmol) and fumaric acid (230 mg, 1.98 mmol) were employed, and the reaction was heated at 140 °C for 48 h. FCC (30% EtOAc/hexane) was followed by further FCC (30% Et_2O/hexane) to provide the title compound as an orange oil indicating the presence of residual rhodium. The crude product was treated with a single drop of DMSO and purified by FCC (10% EtOAc/CH_2Cl_2) to provide the title compound (387 mg, 31%) as a light yellow oil; ν_{max} / cm^{-1}: 2955 (w), 1710 (s), 1656 (s), 1379 (m), 833 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20 (2H, m, C**14**-H), 7.07 (1H, m, C**15**-H), 6.95 (2H, m, C**13**-H), 6.10 (1H, dd, *J* = 7.5, 1.0 Hz, C**7**-H), 5.08 (1H, dd, *J* = 9.0, 7.5 Hz, C**6**-H), 3.41 (1H, m, C**5**-H), 3.07 (3H, s, C**8**-H_3), 2.74 (1H, ddd, *J* = 13.5, 12.0, 1.5 Hz, 1 × C**2**-H_2), 2.63 (1H, m, 1 × C**3**-H_2), 2.54 (1H, m, 1 × C**2**-H_2), 2.45 (1H, m, 1 × C**3**-H_2), 2.04 (2H, s, C**11**-H_2), 1.08 (1H, dd, *J* = 15.0, 6.0 Hz, 1 × C**11**-H_2), 0.83 (1H, dd, *J* = 15.0, 8.0 Hz, 1 × C**11**-H_2), -0.07 (3H, s, C**10**-H_3), -0.07 (3H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.8 (C**4**), 172.9 (C**1**), 139.6 (C**12**), 131.5 (C**7**), 128.4, 128.2 (C**13**, C**14**), 127.0 (C**6**), 124.4 (C**15**), 45.4 (C**5**), 38.8 (C**3**), 34.0 (C**8**), 32.8 (C**2**), 26.1 (C**11**), 15.6 (C**9**), -2.6, -2.9 (C**10**, C**10**); HRMS: (ESI^+) Calculated for $C_{18}H_{25}NNaO_2Si$: 338.1547. Found $[M + Na]^+$: 338.1542.



General Procedure I for the (7+1) carbonylative cycloaddition of *cis*-517: Acrylamide (144 mg, 0.50 mmol), $[Rh(cod)_2]OTf$ (17.6 mg, 0.0375 mmol), $As(PPh_3)_3$ (23.0 mg, 0.0375 mmol) and fumaric acid (29.2 mg, 0.25 mmol) were employed, and the reaction was heated at 140 °C for 48 h. ^1H NMR analysis of the crude reaction mixture against 1,4-DNB as an internal standard indicated formation of the title compound (30% yield).

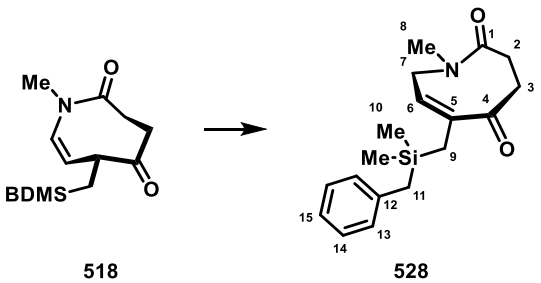
(*Z*)-6-(Hydroxymethyl)-1-methyl-1,3,4,6-tetrahydroazocine-2,5-dione (526)



518 **526**

TBAF (0.16 mL, 0.160 mmol) was added to a stirring solution of silane **518** (34 mg, 0.055 mmol) in THF (0.2 mL) at 0 °C. Upon consumption of silane **518**, as determined by TLC, MeOH (0.18 mL), aq. 30% H_2O_2 (0.088 mL) and $KHCO_3$ (11 mg, 0.110 mmol) were added. The reaction was stirred for 30 minutes before being diluted with water (1 mL) and extracted with EtOAc (5 × 1.5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (90% EtOAc/hexane) provided the title compound (10 mg, 50%) as a colourless oil; ν_{max} / cm^{-1}: 3300 (br.), 2960 (s), 2932 (s), 2874 (s), 1708 (m), 1643 (s), 1462 (s), 1381 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.28 (1H, dd, *J* = 7.5, 1.0 Hz, C**7**-H), 5.45 (1H, dd, *J* = 8.5, 7.5 Hz, C**6**-H), 3.80–3.79 (2H, m, C**9**-H_2), 3.55 (1H, m, C**5**-H), 3.08 (3H, s, C**8**-H_3), 2.84–2.72 (2H, m, 1 × C**2**-H_2, 1 × C**3**-H_2), 2.60–2.48 (2H, m, 1 × C**2**-H_2, 1 × C**3**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.7 (C**4**), 172.6 (C**1**), 133.7 (C**7**), 120.2 (C**6**), 61.8 (C**9**), 51.3 (C**5**), 39.3 (C**2**/**3**), 33.9 (C**8**), 32.2 (C**2**/**3**); HRMS: (ESI^+) Calculated for $C_9H_{14}NO_3$: 184.0968. Found $[M + H]^+$: 184.0975.

(*E*)-6-((Benzyldimethylsilyl)methyl)-1-methyl-1,3,4,8-tetrahydroazocine-2,5-dione (528)

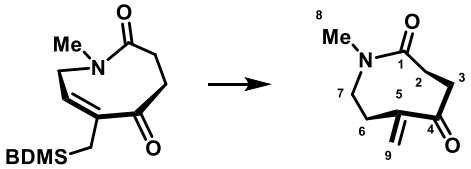


518 **528**

General Procedure J: Enamide **518** (96.2 mg, 0.30 mmol) was employed. FCC (35% EtOAc/hexane) provided ketone (94.0 mg, 68%) as a colourless oil. *The intermediate β-bromide was not characterised at this point*. **General Procedure K:** Bromoketone **527** (23.1 mg, 0.058 mmol) and DBU (0.043 mL, 0.29 mmol) were employed. The reaction was quenched after approximately 30 minutes. FCC (90%

EtOAc/hexane) provided the title compound (10.3 mg, 56%) as a pale yellow oil; ν_{max} / cm^{-1}: 2959 (w), 1681 (m), 1642 (s), 1246 (s), 1057 (s), 831 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21 (2H, m, C**14**-H), 7.08 (1H, m, C**15**-H), 6.98 (2H, m, C**13**-H), 5.73 (1H, t, *J* = 6.5 Hz, C**6**-H), 3.88 (2H, d, *J* = 6.5 Hz, C**7**-H_2), 2.91 (3H, s, C**8**-H_3), 2.84–2.78 (4H, m, C**2**-H_2, C**3**-H_2), 2.12 (2H, s, C**11**-H_2), 1.67 (2H, s, C**9**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.7 (C**4**), 172.4 (C**1**), 144.8 (C**5**), 139.6 (C**12**), 128.4 (C**14**), 128.3 (C**13**), 124.4 (C**15**), 124.2 (C**6**), 48.9 (C**7**), 41.8 (C**2**/**3**), 35.2 (C**8**), 32.1 (C**2**/**3**), 25.9 (C**11**), 23.0 (C**9**), -3.0 (C**10**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{25}NNaO_2Si$: 338.1547. Found $[M + Na]^+$: 338.1554.

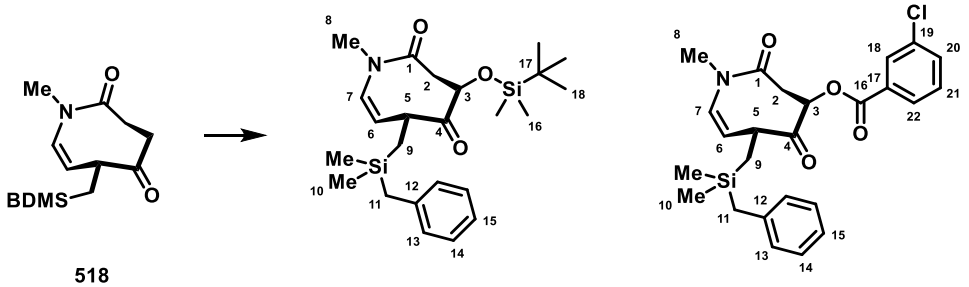
1-Methyl-6-methyleneazocane-2,5-dione (530)



528 530

TBAF (0.16 mL, 0.16 mmol) was added to a stirring solution of silane **528** (10.3 mg, 0.033 mmol) in THF (0.11 mL) at 0 °C. Upon consumption of silane **528**, as determined by TLC, MeOH (0.066 mL), aq. 30% H_2O_2 (0.053 mL) and $KHCO_3$ (9.9 mg, 0.099 mmol) were added. The reaction was stirred for 30 minutes before being diluted with water (1 mL) and extracted with EtOAc (5 × 1.5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. No further purification was carried out. *The reaction provided a mixture of several species resulting from proto-desilylation, which were not identified*; ν_{max} / cm^{-1}: 2924 (m), 2858 (w), 1694 (s), 1633 (s), 1398 (m), 1156 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.26 (1H, s, 1 × C**9**-H_2), 5.21 (1H, s, 1 × C**9**-H_2), 3.47 (2H, t, *J* = 6.0 Hz, C**7**-H_2), 2.90 (3H, s, C**8**-H_3), 2.88 (2H, m, C**3**-H_2), 2.71 (2H, m, C**2**-H_2), 2.56 (2H, t, *J* = 6.0 Hz, C**6**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.0 (C**4**), 172.8 (C**1**), 148.0 (C**5**), 116.9 (C**9**), 48.7 (C**7**), 43.2 (C**3**), 33.6 (C**8**), 33.6 (C**6**), 31.6 (C**2**); HRMS: (ESI$^+$) Calculated for $C_9H_{14}NO_2$: 168.1019. Found $[M + H]^+$: 168.1021.

(*Z*)-6-((Benzyldimethylsilyl)methyl)-4-((*tert*-butyldimethylsilyl)oxy)-1-methyl-1,3,4,6-tetrahydroazocine-2,5-dione (535a) ***and*** **(*Z*)-6-((Benzyldimethylsilyl)methyl)-1-methyl-2,5-dioxo-1,2,3,4,5,6-hexahydroazocin-4-yl 3-chlorobenzoate (536)**

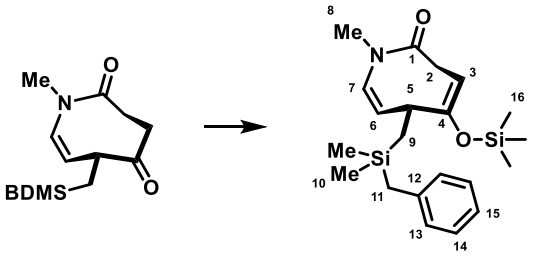


518 535a 536

Freshly prepared LDA (0.96 mL, 0.5 M, 0.48 mmol), DMPU (0.058 mL, 0.48 mmol) and THF (1.6 mL mL) were added to a flame-dried flask fitted with a septum under an atmosphere of argon. The mixture was cooled to -78 °C before the addition of ketone **518** (100 mg, 0.31 mmol) in THF (1 mL) over 1 minute. After 15 minutes, TBSCl (140 mg, 0.93 mmol) in THF (1 mL) was added and the reaction was warmed to room temperature. After 3 h the reaction was quenched with water (5 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. *The crude silyl enol ether was carried through to the Rubottom oxidation step without further purification.* $NaHCO_3$ (29 mg, 0.35 mmol) was added to a flame-dried reaction tube which was sealed and purged with argon. Crude silyl enol ether **534a (**presumed 100% yield in the previous step, 0.31 mmol) in CH_2Cl_2 (3.1 mL) was added by syringe and the reaction mixture was cooled to 0 °C. *m*-CPBA (60.0 mg, 0.35 mmol) in CH_2Cl_2 (1.0 mL) was then added by syringe in one portion. The reaction was stirred for 45 minutes before being diluted with CH_2Cl_2 (5 mL) and washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to provide a mixture of the title compound **535a** and a hemiacetal intermediate. The crude product mixture was dissolved in CH_2Cl_2 (2 mL) and treated with DBU (0.046 mL, 0.031 mmol). The reaction was stirred for 15 minutes before being concentrated *in vacuo* and purified by FCC (30% EtOAc/hexane) to provide the title compounds **535a** and **536** (57 mg, 41%, 1:1 **535a**:**536**) as a colourless oil; *Analytical samples of **535a** and **536** were obtained by further FCC (30% EtOAc/hexane)*; **Data for the TBS-ether 535a:** *The relative stereochemistry of product **535a** was not determined*; ν_{max} / cm^{-1}: 2927 (m), 2860 (m), 1731 (m), 1658 (s), 1378 (m), 1250 (s), 1144 (s), 836 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (2H, m, C**14**-H), 7.08 (1H, m, C**15**-H), 6.95 (2H, d, *J* = 8.0 Hz, C**13**-H), 6.06 (1H, dd, *J* = 7.0, 1.0 Hz, C**7**-H), 5.16 (1H, dd, *J* = 9.0, 7.0 Hz, C**6**-H), 4.42 (1H, dd, *J* = 12.0, 3.5 Hz, C**3**-H), 3.38 (1H, m, C**5**-H), 3.08 (4H, m, 1 × C**2**-H_2, C**8**-H_3), 2.63 (1H, dd, *J* = 12.0, 3.5 Hz, 1 × C**2**-H_2), 2,.03 (2H, s, C**11**-H_2), 1.03 (1H, dd, *J* = 15.0, 6.0 Hz, C**9**-H_2), 0.93–0.90 (10H, m, 1 × C**9**-H_2, 9 × C**18**-H_3), 0.15 (3H, s, C**16**-H_3), 0.06 (3H, s, C**16**-H_3), -0.07 (3H, s, C**10**-H_3), -0.07 (3H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.3 (C**4**), 170.9 (C**1**), 139.5 (C**12**), 131.2 (C**7**), 128.5 (C**14**), 128.1 (C**13**), 127.7 (C**6**), 124.4 (C**15**), 73.9 (C**3**), 43.4 (C**2**), 42.4 (C**5**), 34.0 (C**8**), 26.0 (C**11**), 25.9 (C**18**), 18.6 (C**17**), 16.0 (C**9**), -2.6 (C**10**), -2.8 (C**10**), -4.5 (C**16**), -5.3 (C**16**); HRMS: (ESI^+) Calculated for $C_{24}H_{39}NNaO_3Si_2$: 468.2361. Found $[M + Na]^+$: 468.2354; **Data for the benzoate ester 536:** *The relative stereochemistry of product **536** was not determined*; ν_{max} / cm^{-1}: 2928 (w), 1724 (s), 1659 (s), 1644 (s), 1380 (m), 1290 (s), 1251 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, m, C**18**-H), 7.93 (1H, d, *J* = 8.0 Hz, C**22**-H), 7.55 (1H, d, *J* = 8.0 Hz, C**20**-H), 7.39 (1H, dd, *J* = 8.0, 8.0 Hz, C**21**-H), 7.23 (2H, m, C**14**-H), 7.09 (1H, m, C**15**-H), 6.98 (2H, d, *J* = 8.0 Hz, C**13**-H), 6.11 (1H, d, *J* = 7.5 Hz, C**7**-H), 5.58 (1H, dd, *J* = 13.0, 3.0 Hz, C**3**-H), 5.21 (1H, dd, *J* = 9.0, 7.5 Hz, C**6**-H), 3.47 (1H, m, C**5**-H), 3.26 (1H, dd, *J* = 12.5, 12.0 Hz, 1 × C**2**-H_2), 3.10 (3H, s, C**8**-H_3), 2.85 (1H, dd, *J* = 12.0, 3.0 Hz, 1 × C**2**-H_2), 2.07 (2H, s, C**11**-H_2), 1.14 (1H, dd, *J* = 15.0, 6.5 Hz, C**9**-H_2), 0.91 (1H, dd, *J* = 15.0, 8.0 Hz, C**9**-H_2), -0.01 (3H, s, C**10**-H_3), -0.02 (3H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.4 (C**4**), 169.3

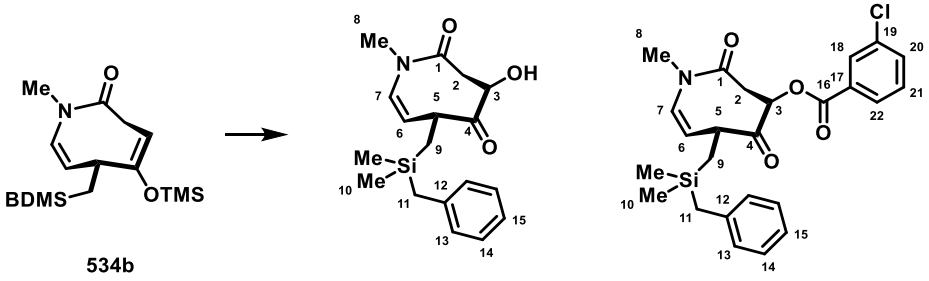
(C**1**), 164.1 (C**16**), 139.5 (C**12**), 134.6 (C**17**/**19**), 133.5 (C**20**), 131.3 (C**7**), 131.2 (C**17**/**19**), 130.0 (C**18**), 129.9 (C**21**), 128.5 (C**14**), 128.1, 128.1 (C**13**, C**22**), 127.8 (C**6**), 124.5 (C**15**), 74.3 (C**3**), 42.7 (C**5**), 38.9 (C**2**), 34.3 (C**8**), 26.1 (C**11**), 15.9 (C**9**), -2.6 (C**10**), -2.9 (C**10**); HRMS: (ESI$^+$) Calculated for $C_{25}H_{28}ClNNaO_4Si$: 492.1368. Found [M + Na]$^+$: 492.1361.

(4*E*,7*Z*)-6-((Benzyldimethylsilyl)methyl)-1-methyl-5-((trimethylsilyl)oxy)-3,6-dihydroazocin-2(1*H*)-one (534b)



Ketone **518** (691 mg, 2.19 mmol) was added to a flame-dried flask equipped with a magnetic stir bar which was sealed with a rubber septum and purged with argon. Dry THF (22 mL, 0.1 M) was added and the solution was cooled to -78 °C. Freshly distilled (Hickman still) TMSCl (0.83 mL, 6.57 mmol) was then added. In a separate flame-dried flask under an atmosphere of argon, *n*-BuLi (3.1 mL, 5 mmol, 1.6 M Hex) was added to a solution of diisopropylamine (0.71 mL, 5.0 mmol) in dry THF (6.2 mL) at 0 °C, over 5 minutes. One equivalent of the freshly prepared LDA solution (4.38 mL, 2.19 mmol, 0.5 M THF) was added to the ketone solution by syringe over 5 minutes. Further LDA solution (typically 0.5 eq.) was then added in 0.1 eq. portions until a suitable end point has been reached as judged by TLC (*Note: A non-polar side-product begins to form before complete consumption of the starting ketone. Therefore, the end point of the reaction is at a time when the starting ketone and unwanted non-polar sideproduct are at a minimum*). The completed reaction mixture was then transferred by syringe to a stirring solution of sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organics are dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was carried through to the next step without further purification due to the instability of the silyl enol ether on silica gel; ν_{max} / cm^{-1}: 2954 (w), 1660 (s), 1375 (m), 1251 (s), 842 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (2H, m, C**14**-H), 7.06 (1H, m, C**15**-H), 6.97 (2H, d, *J* = 7.5 Hz, C**13**-H), 6.11 (1H, d, *J* = 7.5 Hz, C**7**-H), 5.06 (1H, dd, *J* = 9.0, 7.5 Hz, C**6**-H), 4.88 (1H, m, C**3**-H), 3.09–2.99 (2H, m, 1 × C**2**-H_2, C**5**-H), 2.96–2.91 (4H, m, 1 × C**2**-H_2, C**8**-H_3), 2.07 (2H, s, C**11**-H_2), 1.10 (1H, dd, *J* = 15.0, 4.0 Hz, C**9**-H_2), 0.66 (1H, dd, *J* = 15.0, 10.5 Hz, C**9**-H_2), 0.17 (9H, s, C**16**-H_3), -0.02 (3H, s, C**10**-H_3), -0.04 (3H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3 (C**1**), 151.4 (C**4**), 140.0 (C**12**), 129.9 (C**7**), 128.4 (C**14**), 128.2 (C**13**), 125.0 (C**6**), 124.2 (C**15**), 100.4 (C**3**), 36.2 (C**5**), 34.7 (C**2**), 33.0 (C**8**), 26.3 (C**11**), 16.9 (C**9**), 0.3 (C**16**), -2.3 (C**10**), -3.0 (C**10**); HRMS: (ESI$^+$) Calculated for $C_{21}H_{34}NO_2Si$: 388.3123. Found [M + H]$^+$: 388.2123.

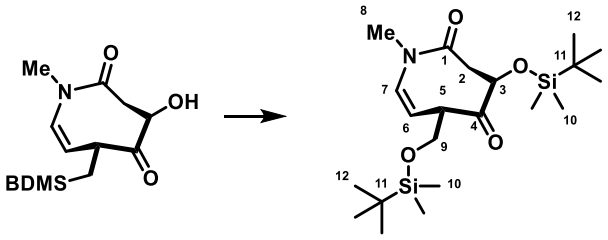
(*Z*)-6-((Benzyldimethylsilyl)methyl)-4-hydroxy-1-methyl-1,3,4,6-tetrahydroazocine-2,5-dione (535b) ***and*** **(*Z*)-6-((Benzyldimethylsilyl)methyl)-1-methyl-2,5-dioxo-1,2,3,4,5,6-hexahydroazocin-4-yl 3-chlorobenzoate (536)**



The crude silyl enol ether **534b** (assumed 100% yield, 1.37 mmol) was dissolved in CH_2Cl_2 (14 mL, 0.1 M) and cooled to 0 °C. *m*-CPBA (353 mg, 1.58 mmol, >77% purity) was added in a single portion and the reaction mixture was warmed to room temperature. On consumption of the starting material as determined by TLC (typically 30 minutes) 10 wt% aq. Na_2SO_3 (10 mL) was added and the mixture was stirred for 10 minutes. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was redissolved in THF (10 mL) and hydrolysed by the addition of 1 M aq. HCl (10 mL) until consumption of the intermediate silyl ether (typically 15 minutes) as determined by TLC. The aqueous layer was extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC (50% EtOAc/hexane) provided the title compound (274 mg, 1:1 d.r., 60%) as a yellow oil and the benzoate ester **536** (48 mg, 7%) as a pale yellow oil. *Although the product diastereomers **535b** are separable at this point, they were carried through as a mixture to the next step to facilitate material throughput*; **Data for the first diastereomer of 535b (A) to elute by FCC:** *The relative stereochemistry of product **535b** was not determined*; ν_{max} / cm^{-1}: 3445 (br.), 2922 (w), 1720 (m), 1657 (s), 1642 (s), 1378 (m), 1249 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.22 (2H, m, C**14**-H), 7.09 (1H, m, C**15**-H), 6.95 (2H, d, *J* = 7.5 Hz, C**13**-H), 6.11 (1H, d, *J* = 7.5 Hz, C**7**-H), 5.15 (1H, dd, *J* = 8.5, 7.5 Hz, C**6**-H), 4.31 (1H, dd, *J* = 9.5, 4.5 Hz, C**3**-H), 3.64 (1H, s, OH), 3.44 (1H, m, C**5**-H), 3.06 (3H, s, C**8**-H_3), 2.84–2.76 (2H, m, C**2**-H_2), 2.05 (2H, s, C**11**-H_2), 1.10 (1H, dd, *J* = 15.0, 6.5 Hz, C**9**-H_2), 0.95 (1H, dd, *J* = 15.0, 8.0 Hz, C**9**-H_2), -0.05 (3H, s, C**10**-H_3), -0.06 (3H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.1 (C**4**), 170.0 (C**1**), 139.4 (C**12**), 132.0 (C**7**), 128.5 (C**14**), 128.1 (C**13**), 126.8 (C**6**), 124.6 (C**15**), 72.1 (C**3**), 42.3 (C**5**), 41.8 (C**2**), 34.2 (C**8**), 26.0 (C**11**), 15.7 (C**9**), -2.5 (C**10**), -2.8 (C**10**); HRMS: (ESI^+) Calculated for $C_{18}H_{26}NO_3Si$: 332.1676. Found $[M + H]^+$: 332.1671; **Data for the second diastereomer of 535b (B) to elute by FCC:** *The relative stereochemistry of product **535b** was not determined*; ν_{max} / cm^{-1}: 3341 (br.), 2922 (m), 1717 (m), 1633 (s), 1249 (m); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21 (2H, m, C**14**-H), 7.08 (1H, m, C**15**-H), 6.97 (2H, d, *J* = 7.5 Hz, C**13**-H), 6.02 (1H, d, *J* = 7.5 Hz, C**7**-H), 5.28 (1H, dd, *J* = 8.0, 7.5 Hz, C**6**-H), 4.25 (1H, dd, *J* = 8.0, 1.5 Hz, C**3**-H), 3.75 (1H, m, C**5**-H), 3.54 (1H, s,

O<u>H</u>), 3.04 (3H, s, C**8**-<u>H</u>$_3$), 2.97 (1H, dd, *J* = 13.0, 1.5 Hz, C**2**-<u>H</u>$_2$), 2.81 (1H, dd, *J* = 13.0, 8.0 Hz, C**2**-<u>H</u>), 2.07 (2H, s, C**11**-<u>H</u>$_2$), 1.15 (1H, dd, *J* = 15.0, 7.5 Hz, C**9**-<u>H</u>$_2$), 0.84 (1H, m, C**9**-<u>H</u>$_2$), -0.03 (6H, s, C**10**-<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.2 (C**4**), 169.9 (C**1**), 139.6 (C**12**), 130.8 (C**7**), 129.5 (C**6**), 128.5 (C**14**), 128.2 (C**13**), 124.4 (C**15**), 70.2 (C**3**), 41.1 (C**5**), 39.4 (C**11**), 34.4 (C**8**), 25.8 (C**11**), 16.1 (C**9**), -2.9 (C**10**), -2.9 (C**10**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{25}NNaO_3Si$: 354.1496. Found [M + Na]$^+$: 354.1489; **Data for the benzoate ester 536:** *The relative stereochemistry of product **536** was not determined*; ν_{max} / cm^{-1}: 2958 (w), 1731 (s), 1660 (s), 1644 (s), 1380 (m), 1247 (s), 1088 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, s, C**18**-<u>H</u>), 7.96 (1H, d, *J* = 8.0 Hz, C**20**/**22**-<u>H</u>), 7.56 (1H, d, *J* = 8.0 Hz, C**20**/**22**-<u>H</u>), 7.40 (1H, dd, *J* = 8.0, 8.0 Hz, C**21**-<u>H</u>), 7.16 (2H, m, C**14**-<u>H</u>), 7.05 (1H, m, C**15**-<u>H</u>), 6.90 (2H, d, *J* = 7.5 Hz, C**13**-<u>H</u>), 6.08 (1H, d, *J* = 7.5 Hz, C**7**-<u>H</u>), 5.31–5.27 (2H, m, C**3**-<u>H</u>, C**6**-<u>H</u>), 3.80 (1H, dt, *J* = 7.5, 7.5 Hz, C**5**-<u>H</u>), 3.18 (1H, dd, *J* = 13.5, 8.5 Hz, C**2**-<u>H</u>$_2$), 3.08 (3H, s, C**8**-<u>H</u>$_3$), 2.98 (1H, d, *J* = 13.5 Hz, C**2**-<u>H</u>$_2$), 2.03 (2H, s, C**11**-<u>H</u>$_2$), 1.16 (1H, dd, *J* = 15.0, 6.5 Hz, C**9**-<u>H</u>$_2$), 0.93 (1H, dd, *J* = 15.0, 8.0 Hz, C**9**-<u>H</u>$_2$), -0.08 (3H, s, C**10**-<u>H</u>$_3$), -0.08 (3H, s, C**10**-<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.8 (C**4**), 167.7 (C**1**), 164.1 (C**16**), 139.4 (C**12**), 134.9 (C**16**/**17**), 133.8 (C**20**/**22**), 131.4 (C**7**), 130.1, 130.1 (C**18**, C**21**), 128.7 (C**6**), 128.4 (C**14**), 128.2 (C**20**/**22**), 128.1 (C**13**), 124.4 (C**15**), 72.2 (C**3**), 41.9 (C**5**), 36.9 (C**2**), 34.5 (C**8**), 25.8 (C**11**), 15.8 (C**9**), -3.0 (C**10**), -3.0 (C**10**); HRMS: (ESI$^+$) Calculated for $C_{25}H_{29}NO_4ClSi$: 470.1549. Found [M + H]$^+$: 470.1542.

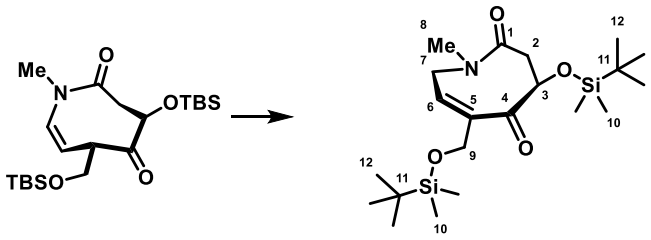
(*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-(((isopropyldimethylsilyl)oxy)methyl)-1-methyl-1,3,4,6-tetrahydroazocine-2,5-dione (539)



UHP (347 mg, 3.69 mmol) was added to a flame-dried flask equipped with a stir bar, which was sealed and purged with argon. Silane **535b** (408 mg, 1.23 mmol) in dry THF (6.2 mL, 0.2 M) was added followed by TBAF (4.9 mL, 4.92 mmol, 1 M THF) over 10 minutes. The reaction mixture was stirred until consumption of the starting material as determined by TLC (10% MeOH/EtOAc). THF (6.2 mL) was then added followed by 10 wt% aq. Na_2SO_3 (5 mL). After 15 minutes solid NaCl was added in order to saturate the aqueous layer which was then extracted with $CHCl_3$ (10 × 10 mL). At this point TLC suggested that a significant quantity of the product remained dissolved in the aqueous layer. The aqueous layer was concentrated *in vacuo* and filtered through a cotton plug washing with MeOH (5 × 5 mL). The combined organics and filtrate were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the crude product and tetrabutylammonium salts. The crude mixture was redissolved in

CH_2Cl_2 (12.4 mL, 0.1 M) before adding imidazole (836 mg, 12.3 mmol), DMAP (30 mg, 0.25 mmol) and TBSCl (926 mg, 6.15 mmol). On completion of the reaction as determined by complete consumption of the diol and mono-TBS intermediates by TLC, sat. aq. $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrate *in vacuo*. Purification by FCC (20% EtOAc/hexane) provided the title compound (155 mg, 29%, 6:1 d.r., A+B) as a colourless crystalline solid; **Data for the 6:1 d.r. mixture of products:** m.p. 82–84 °C (CH_2Cl_2); ν_{max} / cm^{-1}: 2928 (m), 2856 (m), 1736 (m), 1659 (s), 1379 (m), 1252 (m), 1101 (s); HRMS: (ESI^+) Calculated for $C_{21}H_{41}NO_4Si_2$: 428.2647. Found $[M + H]^+$: 428.2656; **Data for the major diastereomer of 539 (A):** ^1H NMR ($CDCl_3$, 500 MHz): δ 6.14 (1H, d, *J* = 7.5 Hz, C**7**-H), 5.18 (1H, dd, *J* = 9.0, 7.5 Hz, C**6**-H), 4.49 (1H, dd, *J* = 12.0, 3.0 Hz, C**3**-H), 4.10 (1H, dd, *J* = 9.0, 9.0 Hz, 1 × C**9**-H_2), 3.59 (1H, m, C**5**-H), 3.54 (1H, dd, *J* = 9.0, 5.5 Hz, C**9**-H_2), 3.06–3.02 (4H, m, 1 × C**2**-H_2, C**8**-H_3), 2.64 (1H, dd, *J* = 12.0, 3.0 Hz, C**2**-H_2), 0.90 (9H, s, C**12**-H_3), 0.83 (9H, s, C**12**-H_3), 0.14 (3H, s, C**10**-H_3), 0.03 (3H, s, C**10**-H_3), 0.02 (3H, s, C**10**-H_3), 0.00 (3H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.7 (C**4**), 170.9 (C**1**), 132.9 (C**7**), 122.0 (C**6**), 74.5 (C**3**), 62.1 (C**9**), 49.5 (C**5**), 43.2 (C**2**), 34.3 (C**8**), 25.9, 25.9 (C**12**), 18.6, 18.3 (C**11**), -4.5, -5.4, -5.4, -5.5 (C**10**); **Data for the minor diastereomer of 539 (B):** *Characteristic signals only*; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.05 (1H, d, J = 7.0 Hz, C**7**-H), 4.41 (1H, dd, J = 12.0, 3.5 Hz, C**3**-H).

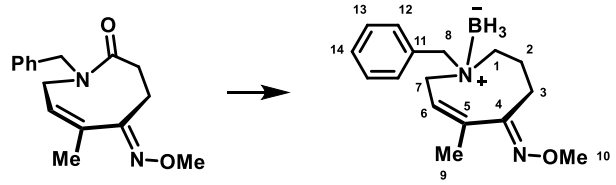
(*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)-1-methyl-1,3,4,8-tetrahydroazocine-2,5-dione (532a)



Enamide **539** (154 mg, 0.36 mmol) in CH_2Cl_2 (3.6 mL, 0.1 M) was added to a flame-dried flask containing $NaHCO_3$ (91 mg, 1.08 mmol) under an atmosphere of argon. The suspension was cooled to 0 °C. Bromine (~1.1 equivalent) was added dropwise by syringe until a brown colour persisted whereby 2,3-dimethylbut-2-ene was added dropwise until the solution became colourless. THF (1.8 mL, 0.2 M) was then added followed by $NaBH_3CN$ (34 mg, 0.54 mmol). The suspension was warmed to room temperature and stirred for 30 minutes before being quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC (25% EtOAc/hexane) provided the intermediate hydrobromination products **540** (128 mg, 70%, mixture of diastereomers) as a colourless oil. *The intermediate hydrobromination products were not characterised at this stage due to them being formed*

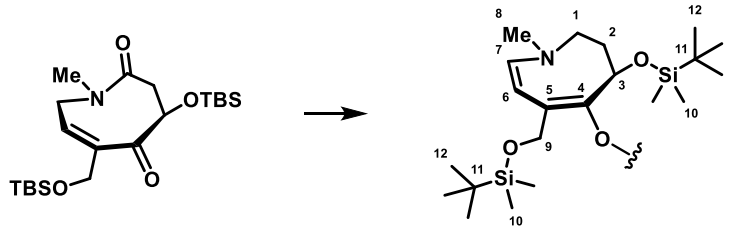
as a mixture of diastereomers and the broad nature of the ^{1}H NMR signals. The hydrobromination products were dissolved in CH_2Cl_2 (2.5 mL, 0.1 M) and DBU (0.11 mL, 0.76 mmol) was added. The reaction was followed closely by TLC to minimise the amount of enamide formed due to isomerisation. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC (40% EtOAc/hexane) provided the title compound (35 mg, 32% over 2 steps) as a colourless oil; ν_{max} / cm^{-1}: 2929 (m), 2856 (m), 1699 (m), 1658 (s), 1462 (m), 1265 (s), 1085 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.02 (1H, m, C**6**-H), 4.44 (1H, dd, *J* = 8.0, 6.5 Hz, C**3**-H), 4.34–4.25 (2H, m, 1 × C**7**-H_2, 1 × C**9**-H_2), 4.18 (1H, m, C**9**-H_2), 3.78 (1H, dd, *J* = 20.0, 6.5 Hz, C**7**-H_2), 2.94–2.83 (5H, m, C**2**-H_2, C**8**-H_3), 0.91 (9H, s, C**12**-H_3), 0.88 (9H, s, C**12**-H_3), 0.09–0.06 (12H, m, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.7 (C**4**), 170.2 (C**1**), 141.7 (C**5**), 123.5 (C**6**), 79.5 (C**3**), 64.2 (C**9**), 50.9 (C**7**), 40.7 (C**2**), 35.8 (C**8**), 26.0, 25.8 (C**12**), 18.5, 18.3 (C**11**), -4.7, -4.8, -5.3, -5.3 (C**10**); HRMS: (ESI^+) Calculated for $C_{21}H_{42}NO_4Si_2$: 428.2647. Found $[M + H]^+$: 428.2658.

(5*E*,6*Z*)-1-Benzyl-6-methyl-1,3,4,8-tetrahydroazocin-5(2*H*)-one *O*-methyl oxime (541)



BH_3·THF (0.44 mL, 0.44 mmol) was added over 5 minutes to a stirring solution of amide **485** (60 mg, 0.22 mmol) in anhydrous THF (2.2 mL) at -78 °C. TLC indicated the reaction was complete after 1.5 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (2 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (10% EtOAc/hexane) provided the title compound (13 mg, 22%) as a colourless oil; ν_{max} / cm^{-1}: 2936 (w), 2379 (br. s), 2279 (w), 1453 (m), 1170 (s), 1034 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (2H, m, 2 × C**12**-H), 7.39–7.31 (3H, m, 2 × C**13**-H, C**14**-H), 5.73 (1H, t, *J* = 8.5 Hz, C**6**-H), 3.92–3.76 (6H, m, 1 × C**7**-H_2, 2 × C**8**-H_2, 3 × C**10**-H_3), 3.31 (1H, dd, *J* = 14.5, 8.5 Hz, 1 × C**7**-H_2), 3.01 (1H, ddd, *J* = 14.0, 5.5, 5.5 Hz, 1 × C**3**-H_2), 2.90–2.76 (2H, m, C**1**-H_2), 2.51–2.28 (2H, m, 1 × C**2**-H_2, 1 × C**3**-H_2), 1.97 (3H, s, C**9**-H_3), 1.76 (1H, m, 1 × C**2**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.1 (C**4**), 142.8 (C**5**), 133.0 (C**12**), 131.8 (C**11**), 129.0 (C**14**), 128.0 (C**13**), 121.7 (C**6**), 66.5 (C**8**), 62.0 (C**10**), 56.3 (C**1**), 55.2 (C**7**), 25.6 (C**3**), 22.3 (C**9**), 21.0 (C**2**); HRMS: (ESI^+) *Mass peak of the borane adduct **541***; Calculated for $C_{16}H_{25}BN_2NaO$: 295.1955. Found $[M + Na]^+$: 295.1967; *Mass peak of the tertiary amine*; Calculated for $C_{16}H_{23}N_2O$: 259.1805. Found $[M + H]^+$: 259.1814.

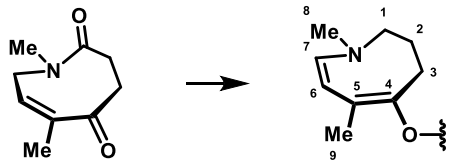
Preliminary data for the product of the reaction of lactam 532a with BH_3·THF (542)



532a **542**

Lactam **532a** (8.5 mg, 0.020 mmol) was added to a flame-dried flask containing a stir bar. Dry THF (0.40 mL, 0.05 M) was added and the reaction was cooled to 0 °C. BH_3·THF (0.06 mL, 0.06 mmol), was added dropwise over 5 minutes and the reaction progress was monitored by TLC. On consumption of the starting material, MeOH (0.4 mL) was added by syringe and the reaction was warmed to room temperature before being concentrated *in vacuo*. FCC provided the unassigned compound (5.1 mg) as a colourless oil. *The structure of the compound **542** has not been fully assigned. The data shown below suggests that the unknown compound contains the structural motif shown above.* ν_{max} / cm^{-1}: 2926 (m), 2856 (m), 1463 (w), 1254 (m), 1063 (s), 837 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.47 (1H, d, *J* = 2.5 Hz, C**7**-H), 5.96 (1H, d, *J* = 2.5 Hz, C**6**-H), 5.17 (1H, dd, *J* = 9.0, 6.5 Hz, C**3**-H), 4.55 (1H, d, *J* = 12.0 Hz, C**9**-H_2), 4.51 (1H, d, *J* = 12.0 Hz, C**9**-H_2), 3.71 (3H, s, C**8**-H_3), 3.61–3.53 (2H, m, 1 × C**1**-H_2, OH), 3.32 (1H, m, C**1**-H_2), 2.22 (1H, m, C**2**-H_2), 1.92 (1H, m, C**2**-H_2), 0.91 (9H, s, C**12**-H_3), 0.86 (9H, s, C**12**-H_3), 0.14 (3H, s, C**10**-H_3), 0.10 (3H, s, C**10**-H_3), 0.06 (3H, s, C**10**-H_3), -0.21 (3H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 130.7 (C**4**), 122.6 (C**7**), 120.4 (C**5**), 107.9 (C**6**), 65.7 (C**3**), 59.4 (C**1**), 58.6 (C**9**), 40.5 (C**2**), 35.4 (C**8**), 26.2, 25.9 (C**12**), 18.6, 18.1 (C**11**), -4.8, -5.1, -5.1, -5.1 (C**10**); HRMS: (ESI^+) Calculated for $C_{21}H_{43}NNaO_3Si_2$: 436.2674. Found $[M + Na]^+$: 436.2671.

Preliminary data for the product of the reaction of lactam 439a with BH_3·THF (544a)

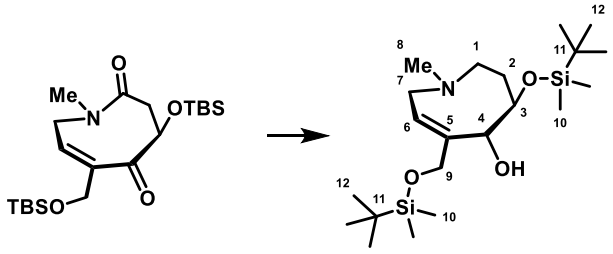


439a **544a**

Lactam **439a** (25 mg, 0.15 mmol) was added to a flame-dried flask containing a stir bar. Dry THF (3.0 mL) was added and the reaction was cooled to 0 °C. BH_3·THF (0.30 mL, 0.30 mmol), was added dropwise over 5 minutes and the reaction progress was monitored by TLC. On consumption of the starting material, MeOH (0.4 mL) was added by syringe and the reaction was warmed to room temperature before being concentrated *in vacuo*. FCC (30% EtOAc/hexane) provided the title compound (11.1 mg, 48%) as a colourless oil; *The structure of the compound **544a** has not been fully*

assigned. The data shown below suggests that the unknown compound contains the structural motif shown above. ν_{max} / cm^{-1}: 3356 (br.), 2923 (s), 2857 (s); ^{1}H NMR (MeOD-d_4, 400 MHz): δ 6.40 (1H, d, *J* = 2.5 Hz, C**7**-H), 5.76 (1H, d, *J* = 2.5 Hz, C**6**-H), 3.55 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 3.51 (3H, s, C**8**-H_3), 2.61 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 1.98 (3H, s, C**9**-H_3), 1.68 (2H, m, C**2**-H_2); ^{13}C NMR (MeOD-d_4, 100 MHz): δ 128.3 (C**4**), 119.3 (C**7**), 114.1 (C**5**), 107.4 (C**6**), 60.9 (C**1**), 32.5 (C**2**), 32.4 (C**8**), 19.8 (C**3**), 10.2 (C**9**); LRMS: (ESI^+) Calculated for $C_9H_{16}NO$: 154.1. Found $[M + H]^+$: 154.1.

(4*R*,5*S*,*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyl-1,2,3,4,5,8-hexahydroazocin-5-ol (545)

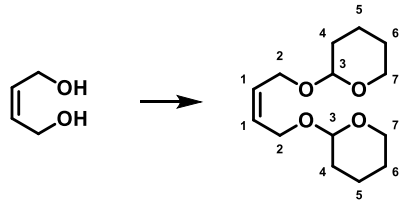


532a **545**

Alane *N*,*N*-dimethylethylamine complex (0.042 mL, 0.021 mmol, 0.5 M PhMe) was added to a stirring soultion of lactam **532a** (6.0 mg, 0.014 mmol) in anhydrous THF (1.0 mL) at 0 °C. TLC indicated that the starting material was consumed in less than 1 minute. The reaction mixture was then quenched by addition of THF:water (1:1, 3 mL) and the resulting solution was concentated *in vacuo*. NMR analysis of the crude reaction mixture indicated the formation of alcohol **545**. *Due to the small quantities involved, several crude reaction mixtures containing alcohol **545** were combined to provide sufficient quantities for characterisation*. The combined crude reactions were purified by FCC (60–100% EtOAc/Hex *then* 30–50% EtOAc/hexane) to provide the title compound of sufficient purity for characterisation. *The relative stereochemistry of product **545** was not determined*; ν_{max} / cm^{-1}: 2956 (s), 2927 (s), 2856 (s), 1467 (m), 1252 (s), 1074 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.69 (1H, m, C**6**-H), 4.17–4.05 (2H, m, C**9**-H_2), 3.94 (1H, ddd, *J* = 10.5, 3.5, 2.5 Hz, C**3**-H), 3.64 (1H, m, C**4**-H), 3.31 (1H, d, *J* = 18.5 Hz, C**7**-H_2), 3.00 (1H, dd. *J* = 18.5, 3.0 Hz, C**7**-H_2), 2.80 (1H, m, C**1**-H_2), 2.35 (3H, s, C**8**-H_3), 2.27 (1H, m, C**1**-H_2), 1.89 (1H, m, C**2**-H_2), 1.68 (1H, m, C**2**-H_2), 0.91 (9H, s, C**12**-H_3), 0.86 (9H, s, C**12**-H_3), 0.07 (3H, s, C**10**-H_3), 0.07 (3H, s, C**10**-H_3), 0.06 (3H, s, C**10**-H_3), 0.04 (3H, s, C**10**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 122.4 (C**6**), 76.7 (C**3**), 73.8 (C**4**), 67.0 (C**9**), 57.5 (C**7**), 55.9 (C**1**), 46.7 (C**8**), 33.2 (C**2**), 26.1, 25.9 (C**12**), 18.6, 18.2 (C**11**), -4.7, -4.7, -5.2, -5.2 (C**10**); HRMS: (ESI^+) Calculated for $C_{21}H_{46}NO_3Si_2$: 416.3011. Found $[M + H]^+$: 416.3022.

4.5 Experimental procedures for the studies in Section 3.3

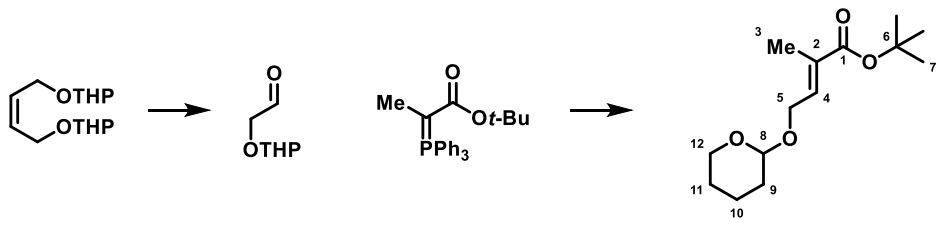
(*Z*)-1,4-Bis((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-ene (I)



601 **I**

Prepared according to a literature procedure.[345] Dihydropyran (4.56 mL, 50.0 mmol, 2.0 eq) was added to a stirring solution of diol **601** (2.06 mL, 25 mmol) and *p*-TSA (28.5 mg, 0.15 mmol) in CH_2Cl_2 (25 mL, 1 M) over 15 minutes (exothermic reaction). The resulting solution was stirred for 1.5 h during which time a blue colour had developed. NEt_3 (0.031 mL, 0.23 mmol) was added by syringe and the reaction mixture was concentrated *in vacuo*. Purification by FCC (50% Et_2O/hexane) provided the title compound (12.4 g, 97%) as a colourless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.74 (2H, t, *J* = 4.0 Hz, 2 × C**1**-H), 4.63 (2H, t, *J* = 3.5 Hz, 2 × C**3**-H), 4.29 (2h, m, 2 × C**2**-H_2), 4.12 (2H, m, 2 × C**2**-H_2), 3.87 (2H, m, 2 × C**7**-H_2), 3.51 (2H, m, 2 × C**7**-H_2), 1.87 (2H, m, 2 × C**5**-H_2), 1.71 (2H, m, 2 × C**4**-H_2), 1.62–1.50 (8H, m, 2 × C**4**-H_2, 2 × C**5**-H_2, 4 × C**6**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 129.3 (C**1**), 98.2 (C**3**), 63.0 (C**2**), 62.4 (C**7**), 30.8 (C**4**), 25.6 (C**6**), 19.6 (C**5**). *The spectroscopic properties of this compound were consistent with that available in the literature*.[345]

***tert*-Butyl (*E*)-2-methyl-4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-enoate (*E*-599a)**

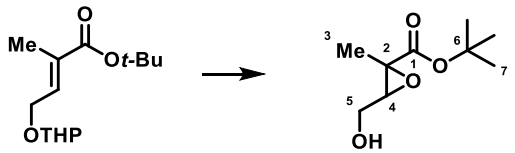


I ***E*-599a**

*Phosphonium ylid **II** was prepared according to a literature procedure.[365] The synthesis of **E*-599a** was adapted from a literature procedure*.[345] A 2-necked Schlenk flask with stopcock was charged with alkene **I** (2.56 g, 10 mmol, 1.0 eq) and DCM (20 mL) and cooled to -78 °C. A tube attached to an ozone generator was passed through a rubber septum and submerged into the reaction mixture. Tubing was attached to the stopcock to guide exhaust gasses to the top of the fumehood. Ozone was passed through the reaction mixture with strong stirring until a faint blue colour appeared or completion was monitored by TLC (approximately 5 h). Nitrogen was then bubbled through the resulting solution for 30 minutes to remove all ozone. PPh_3 (2.62 g, 10.0 mmol) in CH_2Cl_2 (20 mL) were then added and the reaction was

warmed to room temperature and stirred for 2 h. The reaction was concentrated *in vacuo* and purified by FCC (20% EtOAc/hexane) to provide the intermediate aldehyde which was used immediately in the next step. The intermediate aldehyde was dissolved in CH_2Cl_2:PhMe (80 mL, 2:1) and *tert*-butyl ester phosphonium ylide **II** (15.6 g, 40.0 mmol) was added. The reaction was stirred for 16 h before being concentrated *in vacuo*. The crude product was dissolved in Et_2O:Hex (1:1) and filtered to remove PPh_3O and unreacted phosphonium ylide. The filtrate was concentrated *in vacuo* and purified by FCC (10% EtOAc/hexane) to provide the title compound (3.28 g, 64%) as a colourless oil; ν_{max} / cm^{-1}: 2940 (m), 1706 (s), 1656 (w), 1366 (m), 1252 (m), 1135 (s), 1027 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.73 (1H, t, *J* = 6.0 Hz, C**4**-H), 4.65 (1H, t, *J* = 3.5 Hz, C**8**-H), 4.39 (1H, dd, *J* = 14.0, 6.0 Hz, 1 × C**5**-H_2), 4.15 (1H, dd, *J* = 14.0, 6.0 Hz, 1 × C**5**-H_2), 3.87 (1H, m, 1 × C**12**-H_2), 3.53 (1H, m, 1 × C**12**-H_2), 1.85 (1H, m, 1 × C**10**-H_2), 1.81 (3H, s, C**3**-H_3), 1.73 (1H, m, 1 × C**9**-H_2), 1.65–1.51 (4H, m, 1 × C**9**-H_2, 1 × C**10**-H_2, 2 × C**11**-H_2), 1.48 (9H, s, C**7**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.0 (C**1**), 136.8 (C**4**), 131.0 (C**2**), 98.5 (C**8**), 80.5 (C**6**), 64.1 (C**5**), 62.3 (C**12**), 30.7 (C**9**), 28.2 (C**7**), 25.6 (C**11**), 19.5 (C**10**), 12.9 (C**3**); HRMS: (ESI^+) Calculated for $C_{14}H_{24}NaO_4$: 279.1567. Found $[M + Na]^+$: 279.1578.

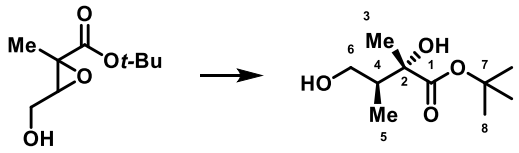
***tert*-Butyl 3-(hydroxymethyl)-2-methyloxirane-2-carboxylate (602)**



***E*-599a** **602**

m-CPBA (25.8 g, 112 mmol, 3.0 eq) was added portion wise over 15 minutes to a stirring solution of alkene ***E*-599a** (9.55 g, 37.0 mmol, 1.0 eq) in CH_2Cl_2 (185 mL, 0.2 M). The reaction was stirred for 48 h by which time TLC (20% Et_2O/hexane) showed consumption of the starting material. Water (50 mL) and sat. aq. Na_2SO_3 (50 mL) were added carefully with vigorous stirring. After an additional 10 minutes of stirring the mixture was transferred to a separating funnel. The organic layer was separated and washed with sat. aq. $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried with $MgSO_4$ and concentrated *in vacuo* to provide the intermediate epoxide. *p*-TSA (70 mg, 0.01 eq) was added to a stirring solution of intermediate epoxide in MeOH (92 mL, 0.4 M). The reaction was stirred for 4 h at which point the intermediate epoxide had been consumed by TLC. NEt_3 (0.11 mL, 0.74 mmol) was added and the reaction was concentrated *in vacuo*. Purification by FCC (30–50% EtOAc/hexane) provided the title compound (4.66 g, 67%) as a colourless oil. ν_{max} / cm^{-1}: 3426 (br.), 2979 (w), 2935 (w), 1725 (s), 1369 (m), 1317 (m), 1156 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.87 (1H, dd, *J* = 12.5, 4.5 Hz, 1 × C**5**-H_2), 3.74 (1H, dd, *J* = 12.5, 6.0 Hz, 1 × C**5**-H_2), 3.37 (1H, dd, *J* = 6.0, 4.5 Hz, C**4**-H), 1.79 (1H, br. s, OH), 1.51 (3H, s, C**3**-H_3), 1.47 (9H, s, C**7**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7 (C**1**), 82.5 (C**6**), 61.3 (C**4**), 60.7 (C**5**), 58.1 (C**2**), 28.0 (C**7**), 13.7 (C**3**); HRMS: (ESI^+) Calculated for $C_9H_{16}NaO_4$: 211.0941. Found $[M + Na]^+$: 211.0944.

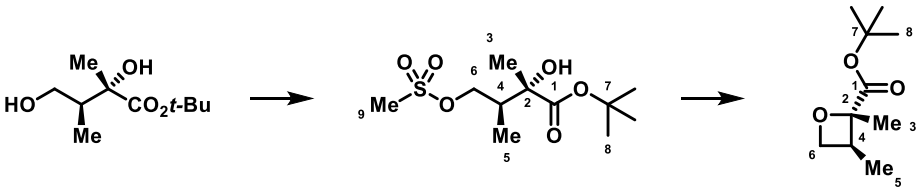
***tert*-Butyl (2*S**,3*S**)-2,4-dihydroxy-2,3-dimethylbutanoate (597a)**



602 597a

A flame dried 3-necked flask was charged with CuI (172 mg, 0.90 mmol) and placed under an atmosphere of nitrogen. THF (18 mL, 0.05 M) was added and the suspension was cooled to -15 °C in an ice/salt bath. MeMgBr (3.0 mL, 9.00 mmol) was added dropwise over 5 minutes before stirring for an additional 30 minutes. Epoxide (170 mg, 0.90 mmol) in THF (3.0 mL) was added dropwise over 10 minutes. After 15 minutes, TLC indicated the reaction was complete. Sat. aq. NH_4Cl (10 mL) was added carefully and the reaction was stirred for 30 minutes before being filtered through celite, washing with Et_2O. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (40% Et_2O/hexane) provided the title compound (129 mg, 70%) as a colourless oil; ν_{max} / cm^{-1}: 3424 (br.), 2977 (w), 2933 (w), 1717 (s), 1456 (m), 1369 (s), 1150 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 3.64 (1H, dd, *J* = 11.0, 6.0 Hz, 1 × C**6**-$\underline{H}_2$), 3.59 (1H, dd, *J* = 11.0, 4.5 Hz, 1 × C**6**-$\underline{H}_2$), 3.44 (1H, br. s, O$\underline{H}$), 2.21 (1H, br. s, O$\underline{H}$), 2.07 (1H, m, C**4**-$\underline{H}$), 1.49 (9H, s, C**8**-$\underline{H}_3$), 1.33 (3H, s, C**3**-$\underline{H}_3$), 1.04 (3H, d, *J* = 7.0 Hz, C**5**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.8 (C**1**), 82.8 (C**7**), 77.4 (C**2**), 65.5 (C**6**), 41.7 (C**4**), 28.0 (C**8**), 24.1 (C**3**), 11.2 (C**5**); HRMS: (ESI^+) Calculated for $C_{10}H_{20}NaO_4$: 227.1254. Found $[M + Na]^+$: 227.1257.

***tert*-Butyl (2*S**,3*S**)-2,3-dimethyloxetane-2-carboxylate (604)**

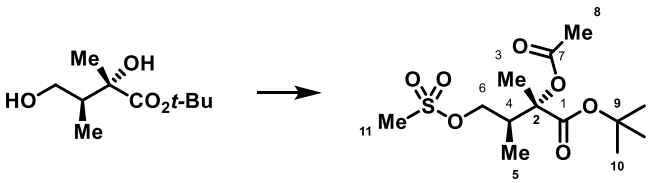


597a 604

MsCl (0.050 mL, 0.65 mmol) was added to a stirring solution of alcohol **597a** (111 mg, 0.54 mmol) and NEt_3 (0.114 mL, 0.82 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C. TLC indicated consumption of the starting material after 15 minutes. Water (5 mL) was added and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Meanwhile, TEPA (0.214 mL, 1.08 mmol) was added dropwise over 10 minutes to a stirring solution of NaH (32 mg, 0.81 mmol) in THF (2.16 mL) at 0 °C. The reaction was stirred for 30 minutes before addition of the crude mesylate in THF (1.5 mL). The reaction was heated at reflux for 3 h at which point a new non-polar spot and the mesylate were visible by TLC. The reaction was cooled to room temperature

before being quenched by the addition of 1 M aq. HCl (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (30% EtOAc/hexane) provided the title oxetane (40 mg, 30%) as a colourless oil; ν_{max} / cm^{-1}: 2979 (m), 1744 (s), 1725 (s), 1368 (m), 1167 (m), 1138 (s), 1121 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.61 (1H, dd, *J* = 8.0, 5.5 Hz, 1 × C**6**-$\underline{H}_2$), 4.07 (1H, dd, *J* = 6.5, 6.0 Hz, 1 × C**6**-$\underline{H}_2$), 3.09 (1H, m, C**4**-$\underline{H}$), 1.48 (9H, s, C**8**-$\underline{H}_3$), 1.44 (3H, s, C**3**-$\underline{H}_3$), 1.18 (3H, d, *J* = 7.0 Hz, C**5**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.1 (C**1**), 86.6 (C**2**), 81.3 (C**7**), 73.6 (C**6**), 36.0 (C**4**), 28.1 (C**8**), 19.2 (C**3**), 13.7 (C**5**); HRMS: (ESI^+) Calculated for $C_{10}H_{18}NaO_3$: 209.1148. Found $[M + Na]^+$: 209.1155.

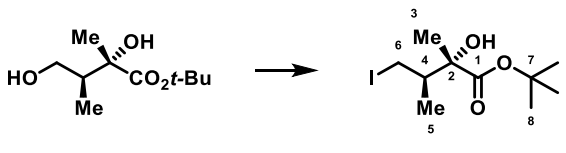
***tert*-Butyl (2*S**,3*S**)-2-acetoxy-2,3-dimethyl-4-((methylsulfonyl)oxy)butanoate (605)**



597a **605**

MsCl (0.149 mL, 1.93 mmol) was added to a stirring solution of alcohol **597a** (328 mg, 1.61 mmol) and NEt_3 (0.336 mL, 2.41 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C. TLC indicated consumption of the starting material after 15 minutes. Water (5 mL) was added and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Ac_2O (1.52 mL, 16.1 mmol) was added to a stirring solution of the crude mesylate and DMAP (49 mg, 0.40 mmol) in pyridine (8.0 mL). The reaction was stirred for 16 h before being diluted with water (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were washed with sat. aq. $CuSO_4$ (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (40% Et_2O/hexane) provided the title compound (255 mg, 49%) as a yellow oil; ν_{max} / cm^{-1}: 2979 (w), 1737 (s), 1458 (w), 1357 (s), 1248 (s), 1175 (s), 962 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.44 (1H, dd, *J* = 10.0, 4.0 Hz, 1 × C**6**-$\underline{H}_2$), 4.09 (1H, dd, *J* = 10.0, 8.0 Hz, 1 × C**6**-$\underline{H}_2$), 3.02 (3H, s, C**9**-$\underline{H}_3$), 2.35 (1H, m, C**4**-$\underline{H}$), 1.51 (3H, s, C**8**-$\underline{H}_3$), 1.46 (9H, s, C**10**-$\underline{H}_3$), 1.06 (3H, d, *J* = 7.0 Hz, C**5**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7 (C**1**), 169.6 (C**7**), 82.5 (C**9**), 82.2 (C**2**), 70.5 (C**6**), 40.4 (C**4**), 37.5 (C**11**), 27.9 (C**10**), 21.3 (C**8**), 17.8 (C**3**), 11.8 (C**5**); HRMS: (ESI^+) Calculated for $C_{13}H_{24}NaO_7S$: 347.1135. Found $[M + Na]^+$: 347.1138.

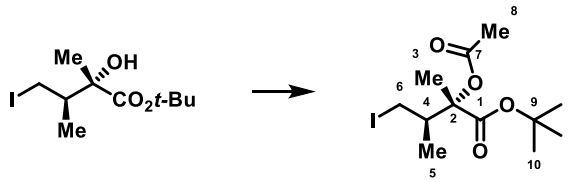
***tert*-Butyl (2*S**,3*R**)-2-hydroxy-4-iodo-2,3-dimethylbutanoate (606a)**



597a **606a**

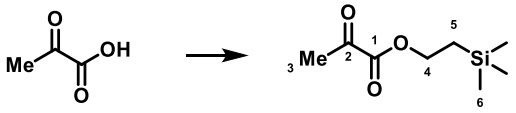
Iodine (635 mg, 2.50 mmol) was added to a solution of PPh_3 (747 mg, 2.85 mmol) and imidazole (464 mg, 6.84 mmol) in CH_2Cl_2 (6.5 mL) at 0 °C and the mixture was stirred for 10 minutes. Alcohol **597a** (465 mg, 2.28 mmol) in CH_2Cl_2 (6.5 mL) was added over 10 minutes and the reaction was warmed to room temperature and stirred for a further 16 h. The reaction was quenched by the addition of $Na_2S_2O_3$ (0.20 g) in water (10 mL) and the organic layer was washed with 1 M aq. HCl (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (5% Et_2O/hexane) provided the title compound (212 mg, 30%) as a colourless oil; ν_{max} / cm^{-1}: 3504 (br.), 2977 (m), 1718 (s), 1369 (m), 1257 (m), 1151 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 3.23 (1H, m, 1 × C**6**-$\underline{H}_2$), 2.92 (1H, dd, *J* = 10.0, 11.0 Hz, 1 × C**6**-$\underline{H}_2$), 2.16 (1H, m, C**4**-$\underline{H}$), 1.51 (9H, s, C**8**-$\underline{H}_3$), 1.34 (3H, s, C**3**-$\underline{H}_3$), 1.15 (3H, dd, *J* = 7.0, 0.5 Hz, C**5**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1 (C**1**), 83.3 (C**7**), 76.5 (C**2**), 44.7 (C**4**), 28.0 (C**8**), 24.3 (C**3**), 14.1 (C**5**), 9.2 (C**6**); HRMS: (ESI^+) Calculated for $C_{10}H_{19}INaO_3$: 337.0271. Found $[M + Na]^+$: 337.0263.

***tert*-Butyl (2*S**,3*R**)-2-acetoxy-4-iodo-2,3-dimethylbutanoate (607a)**



Ac_2O (0.60 mL, 6.30 mmol) was added to a stirring solution of the iodide **606a** (197 mg, 0.63 mmol) and DMAP (20 mg, 0.16 mmol) in pyridine (3.2 mL). The reaction was stirred for 6 h before being diluted with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were washed with sat. aq. $CuSO_4$ (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (5% Et_2O/hexane) provided the title compound (203 mg, 91%) as a colourless oil; ν_{max} / cm^{-1}: 2976 (m), 1737 (s), 1368 (m), 1283 (m), 1246 (s), 1131 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 3.63 (1H, m, 1 × C**6**-$\underline{H}_2$), 2.86 (1H, dd, *J* = 11.0, 9.5 Hz, 1 × C**6**-$\underline{H}_2$), 2.27 (1H, m, C**4**-$\underline{H}$), 2.05 (3H, s, C**8**-$\underline{H}_3$), 1.45 (9H, s, C**10**-$\underline{H}_3$), 1.08 (3H, dd, *J* = 7.0, 0.5 Hz, C**5**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.8 (C**1**), 169.7 (C**7**), 83.3 (C**2**), 82.3 (C**9**), 44.2 (C**4**), 27.9 (C**10**), 21.4 (C**8**), 14.9 (C**5**), 8.0 (C**6**); HRMS: (ESI^+) Calculated for $C_{12}H_{21}INaO_4$: 379.0377. Found $[M + Na]^+$: 379.0390.

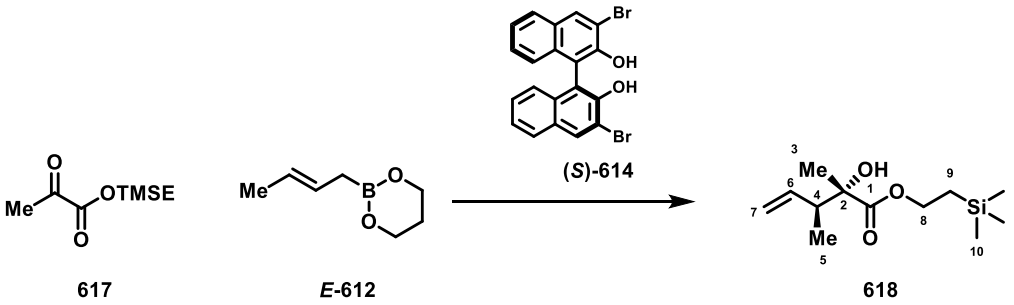
2-(Trimethylsilyl)ethyl 2-oxopropanoate (617)



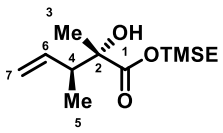
2-(Trimethylsilyl)ethanol (1.28 mL, 10.0 mmol) was added to a stirring solution of pyruvic acid (1.04 mL, 15.0 mmol), EDCI (2.88 g, 15.0 mmol) and DMAP (100 mg, 0.10 mmol) in CH_2Cl_2 (10 mL)

and the reaction was stirred for 16 h. The reaction was concentrated *in vacuo* and purification by FCC (5% EtOAc/hexane) provided the title compound (1.16 g, 62%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.35 (2H, m, C**4**-$\underline{H}_2$), 2.46 (3H, s, C**1**-$\underline{H}_3$), 1.10 (2H, m, C**5**-$\underline{H}_2$), 0.06 (9H, s, C**6**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.3 (C**2**), 161.1 (C**1**), 65.2 (C**3**), 26.8 (C**4**), 17.5 (C**5**), -1.4 (C**6**). *The spectroscopic properties of this compound were consistent with that available in the literature.*[366]

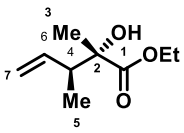
2-(Trimethylsilyl)ethyl (2*S,3*S**)-2-hydroxy-2,3-dimethylpent-4-enoate (618)**



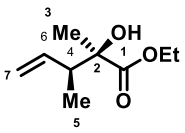
*The crotylation of ketone **617** was adapted from a literature procedure.*[349] *Crotyl boron reagent **E-612**[349] and BINOL-derived catalyst **(S)-614**[367] were prepared according to literature procedures.* A mixture of BINOL-derived catalyst **(*S*)-614** (15 mg, 0.034 mmol), *t*-BuOH (0.325 mL, 3.40 mmol) and crotyl boron reagent ***E*-612** (364 mg, 2.60 mmol) were stirred in PhMe (1 mL) for 5 minutes before the addition of pyruvate ester **617** (320 mg, 1.70 mmol) in PhMe (1 mL). The reaction was stirred at room temperature for 3 h before being concentrated *in vacuo*. FCC (5% EtOAc/hexane) provided the title compound (333 mg, 80%, >25:1 d.r., ~70% e.e., *the two peaks were not fully resolved*) as a colourless oil. *The relative stereochemistry of product **618** was assigned by comparison of the ^{13}C chemical shifts with literature compounds (S*,S*)-**618a** and (S*,R*)-**618a**[368] (see Table S1 below)*; ν_{max} / cm^{-1}: 2955 (w), 1723 (s), 1454 (w), 1250 (s), 1170 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.76 (1H, m, C**6**-$\underline{H}$), 5.04 (1H, m, 1 × C**7**-$\underline{H}_2$), 5.00 (1H, m, 1 × C**7**-$\underline{H}_2$), 4.23 (2H, m, C**8**-$\underline{H}_2$), 3.13 (1H, s, O$\underline{H}$), 2.47 (1H, m, C**4**-$\underline{H}$), 1.36 (3H, s, C**3**-$\underline{H}_3$), 1.07 (3H, d, *J* = 7.0 Hz, C**5**-$\underline{H}_3$), 1.03 (2H, m, C**9**-$\underline{H}_2$), 0.06 (9H, s, C**10**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.2 (C**1**), 139.4 (C**6**), 116.1 (C**7**), 76.4 (C**2**), 64.4 (C**8**), 46.2 (C**4**), 23.7 (C**3**), 17.7 (C**9**), 13.7 (C**5**), -1.4 (C**10**). HRMS: (ESI^+) Calculated for $C_{12}H_{24}O_3Si$: 267.1394. Found $[M + H]^+$: 267.1388. The enantiopurity of this compound was determined by chiral GC (DETA DM Chiraldex G 0605-18, He mobile phase, 0.5 mL/min, 70 °C for 5 min *then* 5 °C/min to 80 °C *then* 2 °C/min to 115 °C *then* 1 °C/min to 135 °C *then* 2 °C/min to 150 °C *then* 5 °C/min to 180 °C) against a racemic standard; t_R (minor) – 32.19 min and t_R (major) – 32.32 min.



(*S**,*S**)-618



(*S**,*S**)-618a

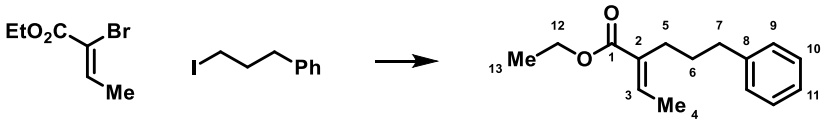


(*S**,*R**)-618a

Carbon number	^{13}C Chemical shift (δ)		
1	**177.2**	**177.1**	177.0
2	**76.4**	**76.5**	76.0
3	**23.7**	**23.7**	24.2
4	**46.2**	46.3	46.2
5	**13.7**	**13.7**	14.2
6	**139.4**	**139.5**	138.5
7	**116.1**	**116.1**	116.7

Table S1: Comparison of the ^{13}C chemical shifts of alkene **618** with literature compounds **(*S**,*S**)-618a** and **(*S**,*R**)-618a**.

Ethyl (*E*)-2-ethylidene-5-phenylpentanoate (624)

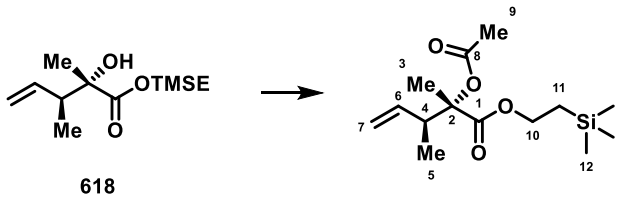


***E*-611** **622** **624**

*α-Bromoacrylate **E-611** was prepared according to a literature procedure*.[369] Zinc dust (255 mg, 3.90 mmol) was added to a flame-dried 5mL flask which was sealed and purged with argon. DMF (0.33 mL) and dibromoethane (0.017 mL, 0.20 mmol) were added and the flask was heated at 50 °C for 20 minutes before being cooled to room temperature. TMSCl (0.005 mL, 0.04 mmol) was added and the reaction was stirred for 30 minutes. Alkyl iodide **622** (0.10 mL, 0.65 mmol) was added and the mixture was stirred for 2 h or until the iodide had been consumed as determined by TLC. Stirring was stopped to allow the solids to settle. $Pd_2(dba)_3$ (11 mg, 0.013 mmol) and SPhos (10.3 mg, 0.025 mmol) was added to a separate flame-dried flask which was sealed and purged with argon. DMF (0.33 mL), α-Bromoacrylate ***E*-611** (96.5 mg, 0.50 mmol) was added to the flask containing the Pd(0)-catalyst followed by the freshly formed alkyl zinc reagent. The reaction was heated at 40 °C for 16 h before being concentrated *in vacuo*. FCC (3% EtOAc/hexane) provided the title compound (40.6 mg, 35%) as a pale yellow oil; ν_{max} / cm^{-1}: 2924 (m), 1707 (s), 1453 (m), 1255 (s), 11645 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.26 (2H, m, ArC<u>H</u>), 7.20–7.15 (3H, m, ArC<u>H</u>), 6.85 (1H, q, *J* = 7.0 Hz, C**3**-<u>H</u>), 4.18 (2H, q, *J* = 7.0 Hz, C**12**-<u>H_2</u>), 2.64 (2H, t, *J* = 8.0 Hz, C**7**-<u>H_2</u>), 2.35 (2H, t, *J* = 8.0 Hz, C**5**-<u>H_2</u>), 1.77–1.69 (5H, m, C**4**-<u>H_3</u>, C**6**-<u>H_2</u>), 1.28 (3H, t, *J* = 7.0 Hz, C**13**-<u>H_3</u>); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.0 (C**1**), 142.4 (C**8**), 137.5 (C**3**), 133.4 (C**2**), 128.5, 128.4, 125.9 (C**9**, C**10**, C**11**), 60.5 (C**12**), 35.9 (C**7**), 30.7

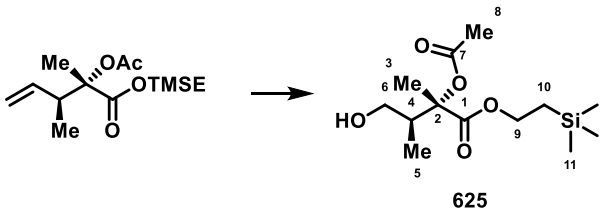
(C**4**), 26.2 (C**5**), 14.4 (C**13**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{20}O_2$: 233.1536. Found [M + H]$^+$: 233.1536.

2-(Trimethylsilyl)ethyl (2*S,3*S**)-2-acetoxy-2,3-dimethylpent-4-enoate**



Ac_2O (1.29 mL, 13.6 mmol) was added to a stirring solution of alcohol **618** (333 mg, 1.36 mmol) and DMAP (42 mg, 0.34 mmol) in pyridine (6.8 mL). The reaction was stirred for 6 h before being diluted with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organics were washed with sat. aq. $CuSO_4$ (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (5% Et_2O/hexane) provided the title compound (337 mg, 86%) as a colourless oil; ν_{max} / cm^{-1}: 2954 (w), 1737 (s), 1370 (m), 1249 (s), 1110 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.86 (1H, m, C**6**-H), 5.12 (1H, d, *J* = 1.0 Hz, 1 × C**7**-H_2), 5.08 (1H, m, 1 × C**7**-H_2), 4.21 (2H, m, C**10**-H_2), 2.65 (1H, m, C**4**-H), 2.05 (3H, s, C**9**-H_3), 1.51 (3H, s, C**3**-H_3), 1.01 (3H, d, *J* = 7.0 Hz, C**5**-H_3), 1.00 (2H, m, C**11**-H_2), 0.04 (9H, s, C**12**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7 (C**1**), 170.1 (C**8**), 137.9 (C**6**), 116.5 (C**7**), 83.0 (C**2**), 63.7 (C**10**), 45.0 (C**4**), 21.4 (C**9**), 17.9 (C**3**), 17.4 (C**11**), 14.1 (C**5**), -1.4 (C**12**); HRMS: (ESI$^+$) Calculated for $C_{14}H_{26}NaO_4Si$: 309.1493. Found [M + Na]$^+$: 309.1506.

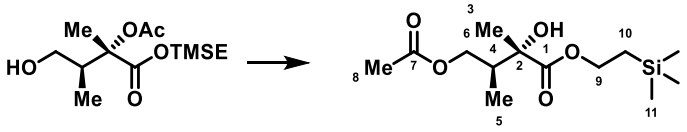
2-(Trimethylsilyl)ethyl (2*S,3*S**)-2-acetoxy-4-hydroxy-2,3-dimethylbutanoate (625)**



A 2-necked Schlenk flask with stopcock was charged with alkene (168 mg, 0.59 mmol) and CH_2Cl_2:MeOH (20 mL, 1:1) and cooled to -78 °C. A tube attached to an ozone generator was passed through a rubber septum and submerged into the reaction mixture. Tubing was attached to the stopcock to guide exhaust gasses to the top of the fumehood. Ozone was passed through the reaction mixture with strong stirring until a faint blue colour appeared or completion was monitored by TLC. Nitrogen was then bubbled through the solution for 30 minutes to remove all ozone. $NaBH_4$ (56 mg, 1.48 mmol) was then added and the reaction was warmed to 0 °C and stirred for 30 minutes. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (25% EtOAc/hexane) to provide the title compound (139 mg, 86%) as a colourless oil; ν_{max} / cm^{-1}: 3457

(br.), 2954 (w), 1738 (s), 1370 (m), 1248 (s), 1129 (m), 1026 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.28–4.16 (2H, m, 2 × C**9**-$\underline{H}_2$), 3.83 (1H, dd, *J* = 11.5, 5.5 Hz, 1 × C**6**-$\underline{H}_2$), 3.54 (1H, dd, *J* = 11.5, 6.0 Hz, 1 × C**6**-$\underline{H}_2$), 2.13 (1H, m, C**4**-$\underline{H}$), 2.07 (3H, s, C**8**-$\underline{H}_3$), 1.57 (3H, s, C**3**-$\underline{H}_3$), 1.03–0.98 (2H, m, C**10**-$\underline{H}_2$), 0.98 (3H, dd, *J* = 7.0, 1.0 Hz, C**5**-$\underline{H}_3$), 0.04 (9H, s, C**11**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0 (C**1**), 169.8 (C**7**), 83.2 (C**2**), 64.3 (C**6**), 64.1 (C**9**), 43.1 (C**4**), 21.5 (C**8**), 18.0 (C**3**), 17.4 (C**10**), 11.9 (C**5**), -1.4 (C**11**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{26}NaO_5Si$: 313.1442. Found [M + Na]$^+$: 313.1453.

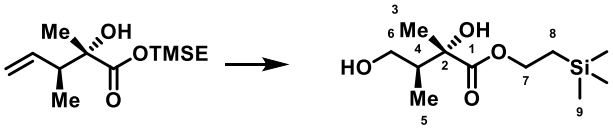
2-(Trimethylsilyl)ethyl (2*S,3*S**)-4-acetoxy-2-hydroxy-2,3-dimethylbutanoate (626)**



625 **626**

Iodine (127 mg, 0.50 mmol) was added to a solution of PPh_3 (149 mg, 0.57 mmol) and imidazole (155 mg, 2.28 mmol) in CH_2Cl_2 (2.3 mL) at 0 °C and the mixture was stirred for 10 minutes. Alcohol **625** (125 mg, 0.456 mmol) in CH_2Cl_2 (2.3 mL) was added over 10 minutes and the reaction was warmed to room temperature and stirred for a further 16 h. The reaction was quenched by the addition of $Na_2S_2O_3$ (0.20 g) in water (10 mL) and the organic layer was washed with 1 M aq. HCl (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (15% Et_2O/hexane) provided the title compound (63 mg, 50%) as a colourless oil; ν_{max} / cm^{-1}: 3506 (br.), 2953 (m), 1725 (s), 1365 (m), 1249 (s), 1176 (m), 1039 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.31 (1H, m, 1 × C**9**-$\underline{H}_2$), 4.22 (1H, m, 1 × C**9**-$\underline{H}_2$), 4.07 (1H, dd, *J* = 11.0, 7.5 Hz, 1 × C**6**-$\underline{H}_2$), 3.90 (1H, dd, *J* = 11.0, 6.5 Hz, 1 × C**6**-$\underline{H}_2$), 3.22 (1H, s, O$\underline{H}$), 2.26 (1H, m, C**4**-$\underline{H}$), 2.26 (3H, s, C**8**-$\underline{H}_3$), 1.36 (3H, s, C**3**-$\underline{H}_3$), 1.04 (2H, m, C**10**-$\underline{H}_2$), 1.00 (3H, d, *J* = 7.0 Hz, C**5**-$\underline{H}_3$), 0.06 (9H, s, C**11**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.5 (C**1**), 170.8 (C**7**), 74.5 (C**2**), 65.9 (C**6**), 64.6 (C**9**), 39.8 (C**4**), 24.6 (C**3**), 21.0 (C**8**), 17.5 (C**10**), 11.2 (C**5**), -1.4 (C**11**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{26}NaO_5Si$: 313.1442. Found [M + Na]$^+$: 313.1453.

2-(Trimethylsilyl)ethyl (2*S,3*S**)-2,4-dihydroxy-2,3-dimethylbutanoate (597b)**

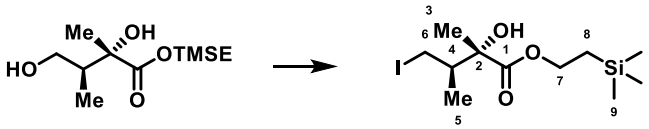


618 **597b**

A 2-necked Schlenk flask with stopcock was charged with alkene **618** (150 mg, 0.60 mmol) and CH_2Cl_2:MeOH (20 mL, 1:1) and cooled to -78 °C. A tube attached to an ozone generator was passed through a rubber septum and submerged into the reaction mixture. Tubing was attached to the stopcock to guide exhaust gasses to the top of the fumehood. Ozone was passed through the reaction mixture with strong stirring until a faint blue colour appeared or completion was monitored by TLC. Nitrogen

was then bubbled through the solution for 30 minutes to remove all ozone. $NaBH_4$ (57 mg, 1.50 mmol) was then added and the reaction was warmed to room temperature and stirred for 3 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (25% EtOAc/hexane) to provide the title compound (40 mg, 27%) as a colourless oil; ν_{max} / cm^{-1}: 3450 (br. m), 2954 (m), 1721 (s), 1250 (s), 1041 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.26 (2H, m, C**7**-$\underline{H}_2$), 3.63 (1H, dd, *J* = 11.0, 6.5 Hz, C**6**-$\underline{H}_2$), 3.57 (1H, dd, *J* = 11.0, 4.5 Hz, C**6**-$\underline{H}_2$), 3.46 (1H, br. s, O$\underline{H}$), 2.11 (1H, m, C**4**-$\underline{H}$), 1.36 (3H, s, C**3**-$\underline{H}_3$), 1.05–1.00 (5H, m, C**5**-$\underline{H}_3$, C**8**-$\underline{H}_2$), 0.05 (9H, s, C**9**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.9 (C**1**), 76.7 (C**2**), 65.4 (C**6**), 64.6 (C**7**), 41.7 (C**4**), 24.0 (C**3**), 17.5 (C**8**), 11.0 (C**5**), -1.4 (C**9**); HRMS: (ESI^+) Calculated for $C_{11}H_{24}NaO_4Si$: 271.1336. Found $[M + Na]^+$: 271.1327.

2-(Trimethylsilyl)ethyl (2*S,3*R**)-2-hydroxy-4-iodo-2,3-dimethylbutanoate (606b)**



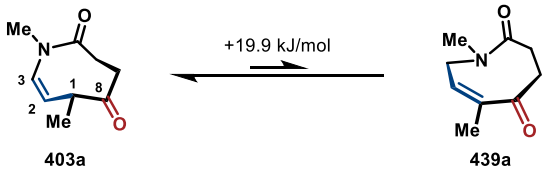
597b **606b**

Iodine (54mg, 0.213 mmol) was added to a solution of PPh_3 (63 mg, 0.242 mmol) and imidazole (40 mg, 0.582 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C and the mixture was stirred for 10 minutes. Alcohol **597b** (24 mg, 0.097 mmol) in CH_2Cl_2 (0.5 mL) was added over 10 minutes and the reaction was warmed to room temperature and stirred for a further 16 h. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ (5 mL) and the organic layer was diluted with CH_2Cl_2 (10 mL), washed with 1 M aq. HCl (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC (2.5% EtOAc/hexane) provided the title compound (14.7 mg, 42%) as a colourless oil; ν_{max} / cm^{-1}: 3513 (br.), 2954 (m), 1721 (s), 1249 (s), 1160 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.29 (2H, m, C**7**-$\underline{H}_2$), 3.22 (1H, dd, *J* = 10.0, 3.0 Hz, C**6**-$\underline{H}_2$), 2.95 (1H, dd, *J* = 10.0, 10.0 Hz, C**6**-$\underline{H}_2$), 2.17 (1H, m, C**4**-$\underline{H}$), 1.38 (3H, s, C**3**-$\underline{H}_3$), 1.15 (3H, d, *J* = 7.0 Hz, C**5**-$\underline{H}_3$), 1.05 (2H, m, C**8**-$\underline{H}_2$), 0.07 (9H, s, C**9**-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.0 (C**1**), 76.5 (C**2**), 65.0 (C**7**), 44.4 (C**4**), 24.1 (C**3**), 17.6 (C**8**), 14.4 (C**5**), 9.0 (C**6**), -1.4 (C**9**); HRMS: (ESI^+) Calculated for $C_{11}H_{23}INaO_3Si$: 381.0353. Found $[M + Na]^+$: 381.0368.

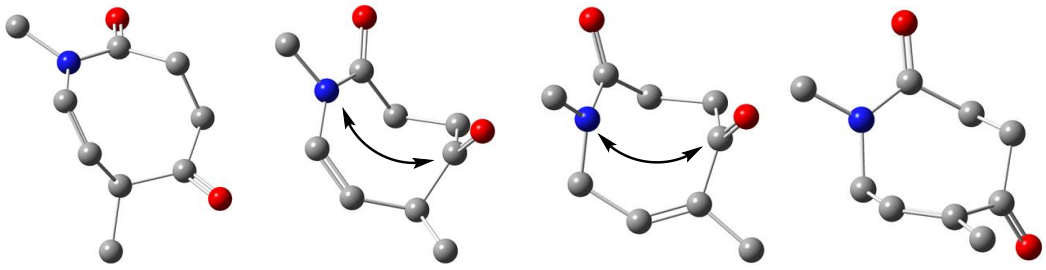
4.6 Computational details

The computational studies in Section 3.2.3.2.2 were carried out with guidance from Dr. Natalie Fey at Bristol. Alkene isomers were subjected to MM conformation distribution searches using the Spartan software to identify low energy conformations. For each alkene isomer, conformations within 10 kJ/mol of the lowest energy conformation were optimised by DFT (B3LYP-6-31g(d))[272-279] using Gaussian 09.[280] The energies of the resulting optimised conformations were compared to give the results shown in Section 3.2.3.2.2. Computed structures were illustrated with Gaussview.[370]

Results from the comparison of 403a and 439a



403a **439a**



BC-403a
boat-chair
0 kJ/mol

BB-403a
boat-boat
+12.7 kJ/mol vs **BC-403a**

BB-439a
boat-boat
+19.9 kJ/mol vs **BC-403a**

CC-439a
chair-chair
+20.3 kJ/mol vs **BC-403a**

BC-403a

B3LYP/6-31G(d) Energy -555.975200272

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	0.346856	1.237850	-1.673760
2	6	0	0.503955	1.633392	-0.666554
3	1	0	0.975066	2.616523	-0.758147
4	6	0	1.530796	0.808074	0.112040
5	7	0	1.712561	-0.518134	-0.251663
6	6	0	0.790940	-1.265912	-1.014535
7	1	0	1.231369	-1.826669	-1.839075
8	6	0	-0.523380	-1.341334	-0.764229
9	1	0	-1.142098	-1.898883	-1.464831
10	6	0	-1.242404	-0.725270	0.417197
11	1	0	-0.503117	-0.552041	1.211083
12	6	0	-0.853683	1.835939	0.043698
13	1	0	-0.662130	2.090240	1.096639
14	1	0	-1.383290	2.680548	-0.405654
15	6	0	-1.805779	0.648067	0.004897

16	8	0	-2.965944	0.779269	-0.335061
17	8	0	2.222219	1.332703	0.976266
18	6	0	2.872353	-1.233547	0.280540
19	1	0	3.281219	-1.884380	-0.500332
20	1	0	2.598681	-1.852778	1.143198
21	1	0	3.620096	-0.504801	0.592289
22	6	0	-2.354674	-1.649427	0.929426
23	1	0	-3.123402	-1.786293	0.163722
24	1	0	-2.840470	-1.219962	1.811420
25	1	0	-1.945646	-2.628077	1.200565

BB-403a

B3LYP/6-31G(d) Energy -555.970355368

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	1.400928	-2.082591	-1.578758
2	6	0	0.784278	-1.292725	-1.143735
3	1	0	0.365607	-0.691405	-1.955220
4	6	0	1.699043	-0.480350	-0.240759
5	7	0	1.331424	0.833335	0.032245
6	6	0	0.342444	1.587137	-0.641972
7	1	0	0.727834	2.542963	-1.000279
8	6	0	-0.952338	1.324352	-0.864152
9	1	0	-1.472216	2.085181	-1.445450
10	6	0	-1.860841	0.184793	-0.446309
11	1	0	-2.182535	-0.316904	-1.374845
12	6	0	-0.335792	-1.928484	-0.291423
13	1	0	-0.984625	-2.535049	-0.938858
14	1	0	0.097079	-2.585771	0.467623
15	6	0	-1.198584	-0.895294	0.423423
16	8	0	-1.396338	-0.952599	1.621052
17	8	0	2.682832	-0.992227	0.276232
18	6	0	2.204428	1.617221	0.910553
19	1	0	1.626610	2.029281	1.743735
20	1	0	2.662198	2.445217	0.353604
21	1	0	2.983870	0.957800	1.288206
22	6	0	-3.110883	0.751075	0.252621
23	1	0	-2.836982	1.216109	1.202603
24	1	0	-3.830743	-0.045539	0.464422
25	1	0	-3.599475	1.499625	-0.380260

BB-439a

B3LYP/6-31G(d) Energy -555.967611771

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.696125	-0.511632	-0.316842
2	7	0	1.365542	0.764820	0.086812
3	6	0	0.504959	1.653612	-0.694568
4	1	0	0.732459	2.673331	-0.363501
5	1	0	0.802097	1.633069	-1.754813

6	6	0	-0.992620	1.475490	-0.599102
7	1	0	-1.534114	2.346140	-0.973916
8	6	0	-1.728667	0.463854	-0.118609
9	6	0	-1.194764	-0.827581	0.460970
10	6	0	0.716184	-1.179207	-1.272833
11	1	0	0.308640	-0.496616	-2.023643
12	1	0	1.255314	-1.975019	-1.791804
13	6	0	-0.421736	-1.795024	-0.434628
14	1	0	-0.030553	-2.584624	0.213648
15	1	0	-1.157938	-2.255712	-1.110579
16	8	0	-1.520248	-1.156061	1.588778
17	8	0	2.634318	-1.135136	0.164461
18	6	0	2.151977	1.379448	1.152996
19	1	0	2.676585	0.589534	1.688596
20	1	0	1.487482	1.914559	1.839317
21	1	0	2.893483	2.084637	0.752696
22	6	0	-3.236395	0.560991	-0.029889
23	1	0	-3.550428	0.456379	1.014387
24	1	0	-3.724918	-0.246597	-0.590981
25	1	0	-3.599845	1.517050	-0.417967

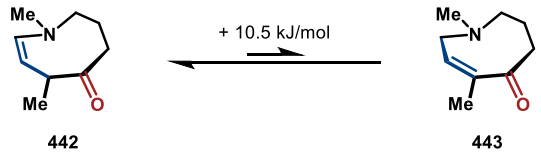
CC-439a

B3LYP/6-31G(d) Energy -555.967464790

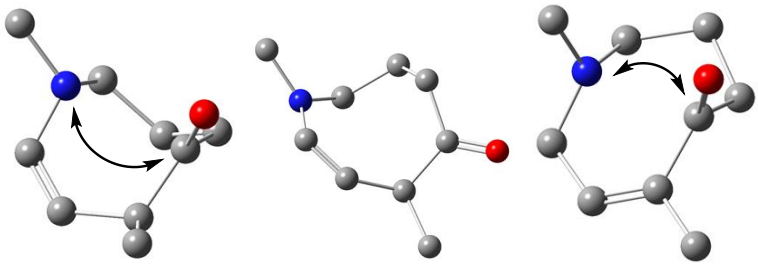
B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.698186	0.761095	-0.143702
2	7	0	1.705777	-0.504821	0.395784
3	6	0	0.560642	-1.038413	1.138304
4	1	0	0.931056	-1.854930	1.767271
5	1	0	0.190627	-0.271810	1.823248
6	6	0	-0.561502	-1.544107	0.253815
7	1	0	-0.534280	-2.599045	-0.017158
8	6	0	-1.574185	-0.795630	-0.201553
9	6	0	-1.733318	0.668967	0.150717
10	6	0	0.654011	1.760240	0.364170
11	1	0	0.517027	1.712769	1.450076
12	1	0	1.089898	2.735759	0.137411
13	6	0	-0.720846	1.696503	-0.354922
14	1	0	-0.546113	1.527928	-1.426124
15	1	0	-1.212453	2.667373	-0.240933
16	8	0	-2.726960	1.028956	0.759076
17	8	0	2.512051	1.111789	-0.992777
18	6	0	2.654553	-1.473543	-0.143266
19	1	0	3.514622	-0.932574	-0.535624
20	1	0	2.217130	-2.066646	-0.958281
21	1	0	2.972552	-2.152633	0.655026
22	6	0	-2.703553	-1.351868	-1.033307
23	1	0	-2.770655	-0.849800	-2.007640
24	1	0	-3.657751	-1.183847	-0.521072
25	1	0	-2.576749	-2.424224	-1.208622

Results from the comparison of 442 and 443



442 443



BB-442
boat-boat

BC-442
distorted boat-chair
+3.4 kJ/mol vs **BB-442**

CC-443
chair-chair
+10.5 kJ/mol vs **BB-442**

BB-442

B3LYP/6-31G(d) Energy -481.932857787

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-1.356669	-0.541259	0.260939
2	6	0	1.574974	-0.227657	-0.539648
3	1	0	1.882937	0.366087	-1.418032
4	6	0	-0.968738	1.556426	-1.010945
5	1	0	-0.555453	1.084102	-1.909361
6	6	0	-1.995019	0.628373	-0.359205
7	1	0	-2.509292	1.168937	0.445530
8	1	0	-2.766500	0.338193	-1.097088
9	1	0	-1.483475	2.464510	-1.349118
10	6	0	1.021360	0.786724	0.483537
11	6	0	0.159162	1.936795	-0.040974
12	1	0	0.842603	2.636952	-0.545706
13	1	0	-0.237281	2.458477	0.836930
14	6	0	-2.241775	-1.261517	1.169068
15	1	0	-1.676681	-2.042398	1.686115
16	1	0	-3.098730	-1.735361	0.653868
17	1	0	-2.633727	-0.569611	1.921383
18	8	0	1.393410	0.770850	1.642317
19	6	0	2.823218	-0.935282	0.017219
20	1	0	2.571213	-1.491380	0.923587
21	1	0	3.599853	-0.209531	0.276813
22	1	0	3.232460	-1.632615	-0.722481
23	6	0	-0.696921	-1.404997	-0.654556
24	1	0	-1.288115	-2.231202	-1.067463
25	6	0	0.574425	-1.250824	-1.035651
26	1	0	0.965477	-1.951386	-1.773158

BC-442

B3LYP/6-31G(d) Energy -481.931561334

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-1.897662	-0.565421	-0.200864
2	6	0	1.386291	-0.639954	-0.370041
3	1	0	1.112075	-0.447645	-1.418304
4	6	0	-0.843507	1.740818	-0.427179
5	1	0	-0.412599	2.376432	-1.213103
6	6	0	-1.450622	0.489364	-1.098581
7	1	0	-2.316457	0.802875	-1.695667
8	1	0	-0.746549	0.047061	-1.805527
9	1	0	-1.653087	2.327959	0.024957
10	6	0	1.485184	0.766210	0.267951
11	6	0	0.203008	1.486916	0.678741
12	1	0	0.515765	2.445304	1.103425
13	1	0	-0.264842	0.904391	1.481816
14	6	0	-3.163706	-0.351561	0.480885
15	1	0	-3.506151	-1.293501	0.921374
16	1	0	-3.919201	-0.020491	-0.240979
17	1	0	-3.112888	0.397683	1.288474
18	8	0	2.567616	1.295174	0.444637
19	6	0	2.764527	-1.315937	-0.393035
20	1	0	3.111867	-1.522151	0.625527
21	1	0	3.508052	-0.674273	-0.870419
22	1	0	2.709232	-2.265428	-0.935853
23	6	0	-0.992950	-1.450423	0.371512
24	1	0	-1.499168	-2.213145	0.961870
25	6	0	0.351843	-1.538180	0.291040
26	1	0	0.776245	-2.392026	0.813612

CC-443

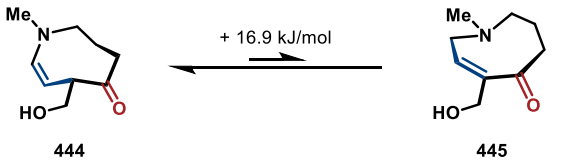
B3LYP/6-31G(d) Energy -481.928840555

B3LYP/6-31G(d) Geometry

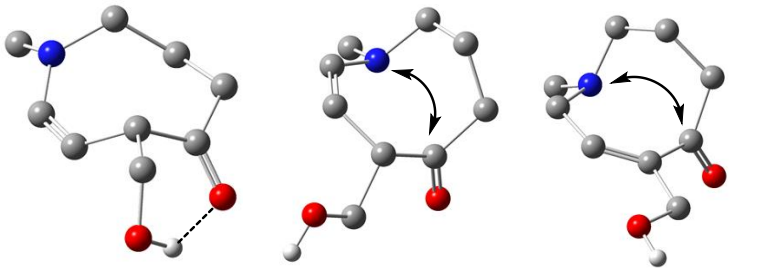
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.705645	0.843460	0.314495
2	6	0	1.583539	-0.296964	-0.172743
3	6	0	1.084573	-1.467963	-0.585160
4	1	0	1.760779	-2.255804	-0.921083
5	6	0	-2.026990	0.119855	-0.700550
6	1	0	-1.938147	-0.148356	-1.760591
7	1	0	-3.087547	-0.003474	-0.428151
8	6	0	-1.579639	1.578032	-0.509263
9	1	0	-1.807766	1.914248	0.509627
10	1	0	-2.121019	2.239512	-1.197847
11	6	0	-0.061220	1.677917	-0.725196
12	1	0	0.197887	1.359642	-1.742873
13	1	0	0.262084	2.718681	-0.602931
14	6	0	-0.392301	-1.796148	-0.589579
15	1	0	-0.745245	-1.925382	-1.624657
16	1	0	-0.552333	-2.773417	-0.105619
17	7	0	-1.172678	-0.766949	0.075921
18	6	0	-1.579987	-1.046082	1.438609

19	1	0	-1.907571	-0.122133	1.924978
20	1	0	-0.723395	-1.418342	2.009222
21	1	0	-2.398322	-1.786122	1.502058
22	6	0	3.062883	-0.009740	-0.093402
23	1	0	3.344275	0.843081	-0.726511
24	1	0	3.659031	-0.874414	-0.401453
25	1	0	3.331939	0.258261	0.935378
26	8	0	0.769384	1.216058	1.479469

Results from the comparison of 444 and 445



444 **445**



BC-444
boat-chair

BB-444
boat-boat
+9.7 kJ/mol vs **BC-444**

BB-445
boat-boat
+16.9 kJ/mol vs **BC-444**

BC-444

B3LYP/6-31G(d) Energy -557.140891635

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	2.126336	-0.779828	-0.209708
2	6	0	1.032823	-1.463294	0.308783
3	6	0	-1.099518	1.037849	0.188865
4	6	0	-0.032172	2.083592	-0.104844
5	1	0	-0.171264	2.404636	-1.149075
6	1	0	-0.252636	2.943484	0.534774
7	6	0	1.440143	1.664332	0.089309
8	1	0	1.603887	1.380030	1.135598
9	1	0	2.043958	2.563544	-0.080775
10	6	0	1.969367	0.531060	-0.836227
11	1	0	1.336757	0.431207	-1.722499
12	1	0	2.959209	0.809759	-1.210970
13	1	0	1.341836	-2.301586	0.929745
14	6	0	-1.093510	-0.265016	-0.618077
15	1	0	-0.654343	-0.072266	-1.603193
16	6	0	-0.297046	-1.300957	0.155010
17	1	0	-0.922121	-1.993059	0.710117
18	6	0	3.392640	-0.967916	0.489236
19	1	0	3.484136	-2.009442	0.809574
20	1	0	3.500861	-0.327238	1.380834
21	1	0	4.224156	-0.749942	-0.189588
22	6	0	-2.540722	-0.757342	-0.856420
23	1	0	-3.095508	0.024824	-1.402356
24	1	0	-2.510097	-1.647861	-1.493466
25	8	0	-1.949275	1.250106	1.045577
26	8	0	-3.208990	-1.128134	0.331068
27	1	0	-3.139090	-0.346918	0.912262

BB-444

B3LYP/6-31G(d) Energy -557.137213254

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	1.564939	-0.741142	0.254046
2	6	0	0.614939	-1.522200	-0.461097
3	6	0	-0.410557	1.128372	0.516379
4	6	0	0.632352	1.976358	-0.211437
5	1	0	0.079348	2.780140	-0.721594
6	1	0	1.246407	2.453973	0.559850
7	6	0	1.506033	1.241598	-1.237628
8	1	0	2.165655	1.960063	-1.740146
9	1	0	0.881884	0.796605	-2.020753
10	6	0	2.368260	0.161778	-0.581748
11	1	0	2.943222	-0.385473	-1.352045
12	1	0	3.098673	0.639680	0.083355
13	1	0	0.945989	-2.512328	-0.796016
14	6	0	-1.282826	0.181946	-0.325760
15	1	0	-1.544841	0.724122	-1.250240
16	6	0	-0.625392	-1.115144	-0.744697
17	1	0	-1.267451	-1.777285	-1.319891
18	6	0	2.372004	-1.545502	1.164818
19	1	0	1.714794	-2.106246	1.835714
20	1	0	3.000192	-0.887625	1.773862
21	1	0	3.029249	-2.265226	0.641080
22	6	0	-2.607717	-0.100916	0.400111
23	1	0	-2.408981	-0.699314	1.298846
24	1	0	-3.055331	0.848646	0.725143
25	8	0	-0.657382	1.316479	1.695052
26	8	0	-3.458941	-0.787076	-0.516827
27	1	0	-4.255372	-1.054700	-0.034938

BB-445

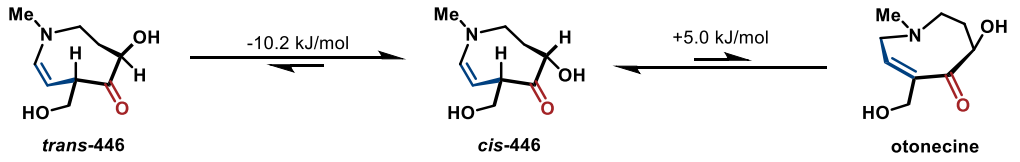
B3LYP/6-31G(d) Energy -557.134465464

B3LYP/6-31G(d) Geometry

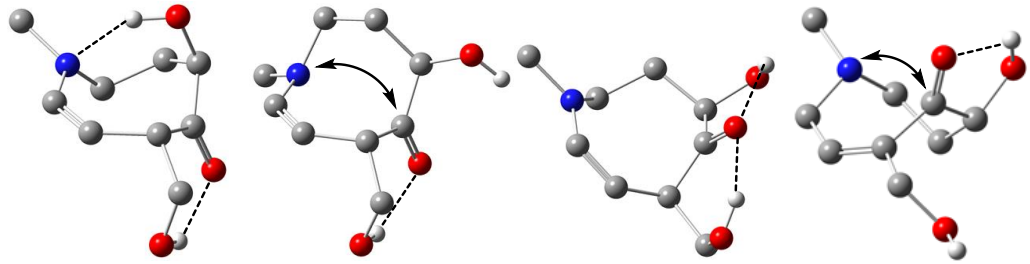
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-2.977864	0.932378	-0.243527
2	6	0	-2.260422	0.279520	-0.756107
3	1	0	-2.830280	-0.291024	-1.516319
4	7	0	-1.670727	-0.596388	0.253152
5	6	0	1.217168	-0.114101	0.043995
6	6	0	0.471663	1.092483	0.565154
7	6	0	-0.366432	1.920352	-0.409880
8	1	0	0.351903	2.563164	-0.942908
9	1	0	-0.990599	2.588053	0.195233
10	6	0	-1.201367	1.149171	-1.436112
11	1	0	-1.702062	1.855449	-2.110105
12	1	0	-0.547290	0.532716	-2.063524
13	6	0	-0.795848	-1.629681	-0.304834
14	1	0	-0.878986	-2.531249	0.317509
15	1	0	-1.139219	-1.945160	-1.309426

16	6	0	0.663597	-1.261761	-0.358964
17	1	0	1.328586	-2.054344	-0.696495
18	6	0	-2.662732	-1.126476	1.181471
19	1	0	-3.214996	-0.297983	1.636634
20	1	0	-2.160595	-1.674628	1.984556
21	1	0	-3.395888	-1.804155	0.703812
22	6	0	2.717180	0.076758	0.101380
23	1	0	2.984923	0.264004	1.153004
24	1	0	2.994547	0.986956	-0.460439
25	8	0	3.385220	-1.061868	-0.419288
26	1	0	4.334898	-0.930280	-0.283819
27	8	0	0.719925	1.519772	1.682680

Results from the comparison of *trans*-446, *cis*-446 and otonecine



***trans*-446** ***cis*-446** **otonecine**



CC-*trans*-446
chair-chair
+10.2 kJ/mol vs **BC-*cis*-446**

BB-*trans*-446
boat-boat
+10.3 kJ/mol vs **BC-*cis*-446**

BC-*cis*-446
boat-chair

BB-otonecine
boat-boat
+5.0 kJ/mol vs **BC-*cis*-446**

CC-*trans*-446

B3LYP/6-31G(d) Energy -632.350263263

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-2.659416	0.193885	-1.719406
2	6	0	-1.719810	0.235342	-1.152795
3	1	0	-0.919803	-0.040901	-1.846455
4	7	0	-1.752699	-0.782362	-0.058759
5	6	0	1.276829	-0.345487	0.684108
6	1	0	0.970154	-0.224858	1.732050
7	6	0	0.877589	0.945210	-0.036471
8	6	0	-0.372615	1.707014	0.448891
9	1	0	-0.056274	2.746695	0.593456
10	6	0	-1.472783	1.659983	-0.636258
11	1	0	-2.378483	2.081321	-0.184757
12	1	0	-1.192229	2.297200	-1.482461
13	6	0	0.576312	-1.573677	0.114245
14	1	0	1.240238	-2.406800	-0.102181
15	6	0	-0.723621	-1.766274	-0.146738
16	1	0	-1.047526	-2.754185	-0.485857
17	8	0	1.514712	1.385924	-0.983927
18	8	0	-0.858894	1.251757	1.697070
19	1	0	-1.312680	0.408265	1.483742
20	6	0	2.808119	-0.527008	0.629754
21	1	0	3.290170	0.356277	1.078981
22	1	0	3.085573	-1.396387	1.236427
23	8	0	3.286446	-0.774967	-0.676779
24	1	0	2.994751	-0.006408	-1.200925
25	6	0	-3.081017	-1.360970	0.154444
26	1	0	-3.070793	-1.988950	1.049981
27	1	0	-3.417721	-1.975437	-0.698449
28	1	0	-3.809201	-0.559695	0.311169

BB-*trans*-446

B3LYP/6-31G(d) Energy -632.350231093

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	1.411729	-1.018861	0.176220
2	6	0	0.716571	-1.536855	-0.954263
3	6	0	-0.562917	0.680808	0.514899
4	6	0	0.565996	1.711129	0.336485
5	1	0	0.984133	1.884126	1.338885
6	6	0	1.673386	1.303284	-0.629689
7	1	0	2.390410	2.128286	-0.710441
8	1	0	1.250608	1.153314	-1.628882
9	6	0	2.383609	0.039710	-0.145997
10	1	0	3.130502	-0.291234	-0.889581
11	1	0	2.928810	0.260167	0.780015
12	1	0	1.178519	-2.381220	-1.477537
13	6	0	-1.217447	0.094773	-0.743187
14	1	0	-1.260029	0.925838	-1.467132
15	6	0	-0.442595	-1.033204	-1.381602
16	1	0	-0.897469	-1.468483	-2.270219
17	6	0	1.962818	-2.075781	1.019719
18	1	0	1.160833	-2.760357	1.309379
19	1	0	2.384417	-1.635503	1.928904
20	1	0	2.755144	-2.659420	0.515923
21	6	0	-2.677320	-0.325145	-0.446331
22	1	0	-3.140684	-0.694996	-1.368237
23	1	0	-3.240458	0.568291	-0.130454
24	8	0	-0.028945	2.909560	-0.177781
25	1	0	-0.636339	3.244382	0.501917
26	8	0	-1.066544	0.540845	1.624312
27	8	0	-2.770066	-1.363059	0.504334
28	1	0	-2.358664	-0.992249	1.306809

BC-*cis*-446

B3LYP/6-31G(d) Energy -632.354131721

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.112199	1.813456	0.349968
2	1	0	-0.237538	1.959315	1.440426
3	6	0	1.370559	1.478288	0.084005
4	1	0	1.911090	2.404225	0.306645
5	6	0	1.164983	-1.615989	-0.434549
6	1	0	1.518651	-2.364575	-1.140456
7	6	0	-0.172681	-1.549222	-0.269761
8	1	0	-0.762263	-2.209813	-0.896831
9	6	0	-1.017675	-0.655493	0.622121
10	1	0	-0.572616	-0.543838	1.617025
11	6	0	-1.111602	0.714464	-0.030551
12	1	0	1.498572	1.296932	-0.989140
13	6	0	1.985429	0.310782	0.900074

14	1	0	2.961898	0.618866	1.284945
15	1	0	1.381856	0.091838	1.785889
16	7	0	2.214287	-0.928213	0.155258
17	6	0	3.499448	-0.991898	-0.532720
18	1	0	3.592010	-0.260230	-1.352838
19	1	0	3.642216	-1.991211	-0.952714
20	1	0	4.309239	-0.807964	0.181249
21	8	0	-1.987448	0.992265	-0.846465
22	6	0	-2.428845	-1.259105	0.823199
23	1	0	-2.327936	-2.206727	1.362286
24	1	0	-3.021986	-0.575888	1.453874
25	8	0	-0.433286	3.001789	-0.329669
26	1	0	-1.222624	2.786852	-0.866252
27	8	0	-3.093906	-1.551565	-0.387605
28	1	0	-3.117959	-0.711907	-0.881710

BB-otonecine

B3LYP/6-31G(d) Energy -632.352237540

B3LYP/6-31G(d) Geometry

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	0.893527	-2.762949	-0.741706
2	6	0	0.407816	-1.849767	-0.395165
3	6	0	-1.098104	-1.835869	-0.464100
4	1	0	-1.478756	-2.720164	0.066067
5	6	0	-0.821828	1.003248	-1.504032
6	1	0	-1.111649	1.840968	-2.148402
7	1	0	-0.310908	0.271243	-2.140149
8	6	0	0.151920	1.513509	-0.439235
9	1	0	1.092180	1.811126	-0.940106
10	6	0	0.591981	0.452443	0.582719
11	6	0	1.157743	-0.855304	0.090574
12	1	0	-1.420331	-1.968504	-1.512652
13	6	0	-2.065280	0.397050	-0.852352
14	1	0	-2.757463	0.006518	-1.621398
15	1	0	-2.586565	1.187674	-0.305589
16	7	0	-1.681193	-0.627500	0.115736
17	6	0	-2.668387	-0.875992	1.157067
18	1	0	-2.237037	-1.526280	1.924760
19	1	0	-3.594935	-1.348278	0.781637
20	1	0	-2.936019	0.071138	1.634930
21	6	0	2.653376	-0.961162	0.231904
22	1	0	2.909260	-0.825303	1.292949
23	1	0	2.994965	-1.959457	-0.080035
24	8	0	3.256253	0.062504	-0.566125
25	1	0	4.126360	0.261215	-0.189190
26	8	0	-0.414767	2.605131	0.252404
27	1	0	-0.133091	2.472034	1.181373
28	8	0	0.716437	0.788939	1.756605

References

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